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LABORATORY AND CLINICAL EXPERIENCE WITH CARBOMYCIN*

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CARBOMYCIN is a new antibiotic substance produced by a soil actinomycete, *Streptomyces halstedii*. The isolation, purification and characterization of its physical and chemical properties have been accomplished by the workers from the Pfizer Research Laboratories.[1] It is a crystalline, monobasic substance containing carbon, hydrogen and nitrogen with a molecular weight of about 860. The free base is only slightly water soluble, but dissolves readily in organic solvents. Acid salts such as the hydrochloride, phosphate or sulfate are prepared readily and are water soluble. Low degrees of both acute and chronic toxicity were noted for animals, including dogs, after both oral and parenteral administration. Because this agent might be useful in the treatment of infections due to gram-positive cocci, notably staphylococci and enterococci, that are resistant to penicillin, aureomycin and terramycin, laboratory studies and clinical trials in human beings were undertaken.§

ANTIBACTERIAL SPECTRUM

In vitro tests have shown the greatest activity of this agent to be against gram-positive bacteria.[1-3] Activity against rickettsias and the large viruses of the psittacosis-lymphogranuloma group is manifested by survival of infected animals treated with carbomycin.[1, 2] Gram-negative bacilli, *Mycobacterium tuberculosis*, yeasts and fungi are resistant with the possible exception of some strains of hemophilus, which are, however, only moderately sensitive. The sensitivity of the gram-positive cocci is of the greatest practical significance, particularly the staphylococci and fecal streptococci. Various strains of these bacteria were obtained directly from cultures of body fluids and exudates and subjected to tube-dilution sensitivity tests. Brain-heart infusion broth (Difco) at pH 7.6 was employed with an inoculum of 0.5 cc. of a 10^{-2} dilution of an eighteen-hour culture to make 1.0 cc. of final volume (Table 1). Of 50 strains of *M. pyogenes* (var. *aureus*) 27 were resistant to a concentration of penicillin over 5 microgm., and 16 to over 5 microgm. of terramycin per cubic centimeter. Only 5 were resistant to a concentration of carbomycin of 5 microgm. per cubic centimeter or more, the majority being sensitive to 1.5 microgm. or less (Fig. 1). Ten per cent of this group, however, were resistant to 5 microgm. per cubic centimeter—a concentration only rarely observed in any body

TABLE 1. *Sensitivity of Bacteria to Carbomycin.*

ORGANISM	NO. OF STRAINS	MINIMUM INHIBITING CONCENTRATION RANGE	MINIMUM INHIBITING CONCENTRATION FOR TWO THIRDS OF STRAINS	NO. OF STRAINS REQUIRING CONCENTRATION OF 5 MICROGM./CC. OR OVER
Micrococcus pyogenes (var. *aureus*)	50	0.39–12.5	1.6	5
Streptococcus faecalis	30	0.16–2.5	0.8	0
Streptococcus viridans	8	0.04–1.6		0
Streptococcus pyogenes	30	0.02–2.5	0.31	0
Diplococcus pneumoniae	20	0.02–0.6	0.08	0
Hemophilus influenzae	8	1.56–12.5		2

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§Generous supplies of carbomycin were made available through the kindness of Drs. Harry Seneca and William Farley, Department of Clinical Investigation, Charles Pfizer and Company, Incorporated, Brooklyn, New York. The trade name adopted for this antibiotic is Magnamycin.

fluid or exudate except urine. All the enterococci tested were sensitive to 2.5 microgm. of carbomycin per cubic centimeter or less (Fig. 2). The pneumococci and alpha-hemolytic and beta-hemolytic streptococci were the most sensitive groups of bacteria.

Mode of Action

Bacteriostatic concentrations of carbomycin were determined by the tube-dilution method for 35 cultures of *M. pyogenes* (var. *aureus*) and

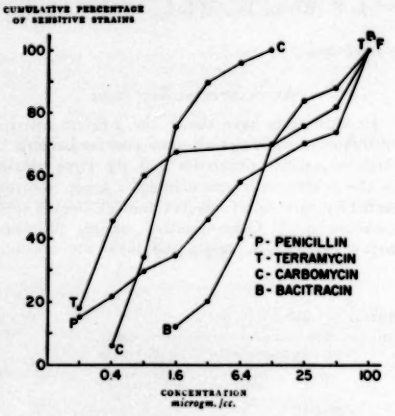

Figure 1 *Sensitivity of 50 Strains of* M. pyogenes (*var.* aureus) *to Carbomycin and Three Other Antibiotics.*

Str. faecalis. The broth from tubes showing no macroscopic growth was streaked on blood-agar plates, or the entire amount of broth was added to melted, cool agar and plates were poured. The plates were incubated, and the bactericidal concentration determined as the least concentration of carbomycin in the tube dilution series that proved to be sterile on subculture by the plate method.

On the basis of plate counts, cultures exposed to even the minimum inhibiting concentration (M.I.C.) of carbomycin showed a marked reduction in the number of bacteria indicating bactericidal activity in vitro. This was much greater than that of terramycin, which was primarily bacteriostatic, but was less than that of penicillin. The minimum bactericidal concentration (M.C.C.) of penicillin was the same as the M.I.C. in 10 cases, twice that of the M.I.C. in 18, and four times that of the M.I.C. in 7. The M.C.C. of carbomycin was four times the M.I.C. in 4 cases, eight times the M.I.C. in 8, sixteen times the M.I.C. in 13 and up to and over a hundred times the M.I.C. in the remaining 10 cultures. The persistence of small numbers of viable bacteria after exposure to carbomycin is shown in Table 2.

Resistance and Cross Resistance

The development of resistance to carbomycin in vitro was studied by serial-transfer procedure in broth employing four strains of *M. pyogenes* (var. *aureus*) and four strains of enterococci. Serial dilutions of carbomycin in 1:2 decreasing concentrations were prepared daily and inoculated with 0.5 cc. of a 10^{-4} dilution of the tube containing the maximum concentration of carbomycin in which growth occurred from the previous day. Transfers were performed every twenty-four hours. Development of resistance to terramycin was studied simultaneously. Sensitivity of all strains to penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, bacitracin and erythromycin* was determined at the beginning and end of the serial-transfer procedure.

The increases in resistance of representative organisms to carbomycin and terramycin after

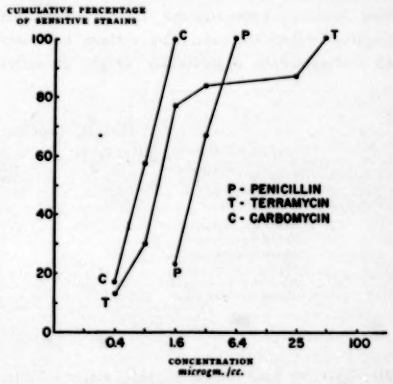

Figure 2. *Sensitivity of 30 Strains of Enterococci to Carbomycin, Penicillin and Terramycin.*

successive transfers are shown in Figure 3. The pattern of development of carbomycin resistance is similar to that of penicillin and terramycin, but occurs more rapidly. No case of explosive mutation of the streptomycin type was observed. It was possible to increase the carbomycin resistance a thousand times during the 36 transfers. No differences were observed in the development of resistance by staphylococci and enterococci.

No cross resistance has been demonstrated between carbomycin and other antibiotic agents except erythromycin, with which cross resistance has been constant.[3, 4] As resistance to carbomycin develops so also does erythromycin resistance (Table 3). As previously noted by Finland,[4] in several cases

*Supplied through the kindness of Dr. J. W. Smith, Lilly Research Laboratories, Indianapolis, Indiana.

the same ratio of sensitivity to carbomycin and erythromycin was preserved as carbomycin resistance increased. Because of the greater antibacterial potency of erythromycin on a weight basis the sensitivity of a culture to that agent in vitro may still be within the range of serum concentration obtainable whereas it may be entirely outside that obtainable with carbomycin.

TABLE 2. *Bacteriostatic and Bactericidal Concentrations of Carbomycin.*

Concentration of Carbomycin	No. of Colonies Appearing on Plates Subcultured from Broth					
	Bowen strain	Brimser strain	Carposo strain	Castillo strain	Daniels strain	Fanning strain
microgm./cc.						
50.0	0	0	3	2	5	0
25.0	0	0*	15	2	1	0
12.5	0*	1	14	2	1	0
6.25	1	1	14	3	1	0
3.12	9	3	18†	7†	4	0
1.6	16†	11	++	++++	13†	0*
0.8	++++	25†	++++	++++	++++	6†
0.4	++++	++++	++++	++++	++++	++++

*M.C.C.
†M.I.C.

PHARMACOLOGY

For the purpose of studies of absorption and excretion, gelatin capsules containing 250 mg. of carbomycin were administered to adult human subjects who presented no evidence of impaired cardiac, renal or hepatic function. At least two doses of the drug at six-hour intervals were administered before specimens were obtained for assay. Intravenous doses of 400 mg. diluted in 20 cc. of physiologic saline solution were administered. Assay was performed by a 1:2 serial dilution technic using a Group A hemolytic streptococcus or a pneumococcus as the test organism. A serum concentration of 0.16 microgm. per cubic centimeter could be detected by this method.

Oral doses of less than 500 mg. usually failed to produce any antibacterial activity in the serum. After 500-mg. doses 80 per cent of the patients showed some antibacterial serum activity an hour after administration (Fig. 4). The highest serum concentration was 1.25 microgm. per cubic centi-

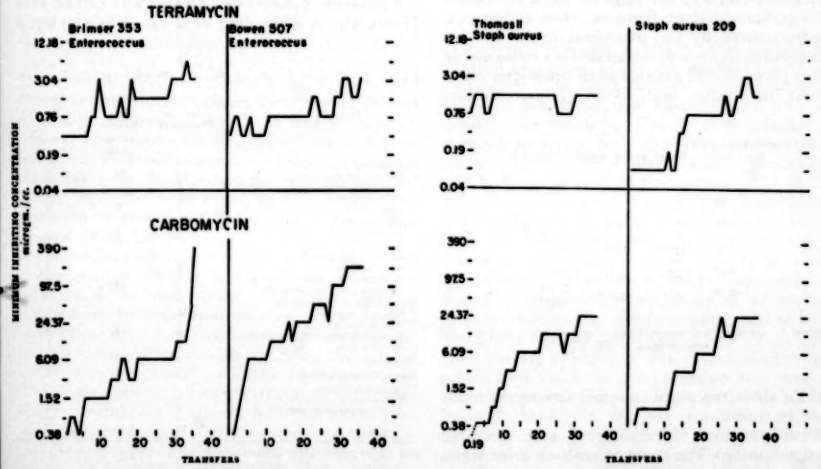

FIGURE 3. *Development of Resistance to Carbomycin and Terramycin by Staphylococci and Enterococci.*

meter, but most patients never showed concentrations higher than 0.31 microgm. Six hours after administration about 20 per cent of the subjects had assayable serum concentrations. Ten patients

TABLE 3. *Development of Resistance after Transfer in Progressively Increasing Concentrations of Carbomycin.*

ORGANISM	M.I.C. IN ORIGINAL CULTURE		M.I.C. IN CULTURE AFTER 30TH PASSAGE	
	CARBOMYCIN microgm./cc.	ERYTHROMYCIN microgm./cc.	CARBOMYCIN microgm./cc.	ERYTHROMYCIN microgm./cc.
M. pyogenes (var. *aureus*)	0.72	0.19	24.0	3.0
M. pyogenes (var. *aureus*)	0.38	0.19	24.0	0.72
M. pyogenes (var. *aureus*)	0.72	0.19	3.0	0.38
M. pyogenes (var. *aureus*)	0.38	0.09	24.0	0.72
Enterococcus	0.38	0.19	390.0	390.0
Enterococcus	0.72	0.19	195.0	6.1
Enterococcus	0.72	0.38	97.5	6.1
Enterococcus	0.72	0.38	3.0	0.72

receiving 750-mg. doses demonstrated no significant increase in serum concentrations.

The median serum concentration of 0.63 microgm. per cubic centimeter an hour after intravenous administration of 400 mg. was significantly higher than 0.16 microgm. after 500 mg. orally (Fig. 5). Although the maximum concentration of 2.5 microgm. per cubic centimeter after intravenous administration did not significantly exceed that after oral administration, it is apparent that concentrations over 0.31 microgm. per cubic centimeter are significantly more frequent when carbomycin is administered by the parenteral route.

Serum activity was demonstrable in a considerably higher proportion of patients at all times after intravenous than after oral administration. Almost

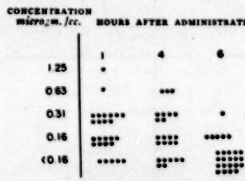

FIGURE 4. *Serum Carbomycin Concentrations after the Oral Administration of 500 Mg.*

half the subjects showed no serum activity six hours after injection.

Small amounts of carbomycin were recovered from the urine. The twenty-four-hour urine specimens collected from 20 patients on doses of 2 gm. daily showed amounts of carbomycin representing 0.1 to 1.3 per cent of the ingested daily dose. The concentrations in the urine of these patients varied from 0.625 to 20.0 microgm. per cubic centimeter. After intravenous administration of 400 mg. to 3 patients urinary concentrations were as high as 137 microgm. per cubic centimeter thirty minutes after injection, and serum concentrations were 1.25 to 2.5 microgm. Three hours after injection urine concentrations were 1.25 to 6.25 microgm., and urinary excretion declined rapidly. Four hours after injection no antibacterial activity was demonstrable in the urine of 2 of the 3 subjects. The mean

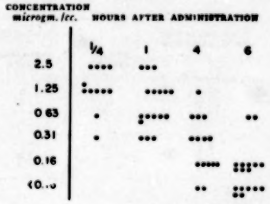

FIGURE 5. *Serum Carbomycin Concentrations after the Intravenous Injection of 400 Mg.*

total amount of a single intravenous dose recovered from the urine was 2.5 per cent.

Diffusibility across uninflamed meninges was not observed in 5 patients studied.

CLINICAL RESULTS

Fifty-seven patients were treated with carbomycin (Table 4). A daily dose of 2 gm. was employed

TABLE 4. *Clinical Results in Patients Treated with Carbomycin.*

DISEASE	NO. OF PATIENTS	GOOD RESULT	NO EFFECT
		NO. OF CASES	NO. OF CASES
Pneumonia:			
Pneumococcal	12	10	2
H. influenzae	2		2
Staph. aureus	3		3
Nonspecific	7	6	1
Acute bronchitis:			
Pneumococcal	1	1	
Nonspecific	7	6	1
Bacterial endocarditis:			
Enterococcus	2		2
Nonhemolytic streptococcus	2		2
M. pyogenes (var. *aureus*)	2	1(?)	1
Tonsillitis and pharyngitis:			
Fusospirochetal	1	1	
Pneumococcal	1		1
Beta-hemolytic streptococcus	3	1	2
H. influenzae	1		1
Amebiasis	5	5	
Staphylococcal sepsis	2	1	1
Urinary infections:			
Enterococcus	4	2	2
M. pyogenes (var. *aureus*)	2		2
Totals	57	34	23

except for several acutely ill patients, to whom 3-gm. daily doses were administered for several days or to whom 400-mg. doses were given intravenously at intervals of six to eight hours for periods of twenty-four to ninety-six hours.

Pneumonia

In 21 cases of pneumonia, *D. pneumoniae* was isolated from the sputum of 12 patients and the blood of 4. No previous antibiotic therapy had been administered to these patients, and carbomycin was instituted on the first to the eighth day after the onset of illness. The total dose varied from 11.0 to 14 gm., and the duration of therapy from five to eight days. Pneumococci persisted in the sputum twenty-four hours after institution of chemotherapy in 3 cases. After forty-eight hours of treatment pneumococci persisted in 1 patient, described below as a treatment failure; 10 of the 12 showed a prompt response of fever, the longest duration of fever after institution of therapy being four days. Satisfactory amelioration of clinical symptoms, signs and x-ray findings occurred in a manner consistent with that to be expected after therapy with penicillin or one of the broad-spectrum antibiotic agents (Fig. 6).

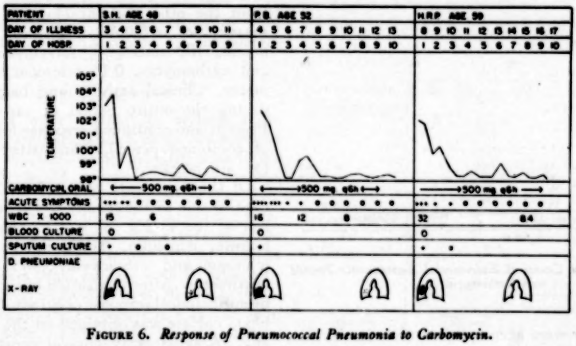

FIGURE 6. *Response of Pneumococcal Pneumonia to Carbomycin.*

One of the patients who failed to respond showed predominantly Proteus species in the sputum in addition to *D. pneumoniae*. The latter organism disappeared from the sputum after two and a half days of carbomycin without any evidence of clinical improvement. Prompt defervescence and clinical improvement followed institution of streptomycin. The single clear-cut failure of carbomycin in pneumococcal pneumonia occurred in a sixty-four-year-old disoriented man with pneumonia of the right middle and upper lobes associated with severe acute sepsis, a white-cell count of 2600, with many immature neutrophils, and bacteremia. Carbomycin was administered parenterally in a daily dose of 1600 mg. for three days, during which the sepsis failed to improve clinically and pneumococci continued to be present in the sputum. In spite of institution of penicillin the patient died on the fourth day of hospitalization. At autopsy consolidation of the right upper and middle lobes was present, and *D. pneumoniae* was isolated from the lung.

Eight patients presented a clinical and roentgenologic picture of bacterial pneumonia that could not be ascribed to the pneumococcus. The sputum of 1 showed many colonies of *H. influenzae* and that of 2 others many colonies of *M. pyogenes* (var. *aureus*) in almost pure culture. One patient had received penicillin before admission without improvement. The total dose varied from 10 to 22 gm., and the duration of therapy from four and a half to eleven days. Five of these patients responded promptly both clinically and roentgenologically in a manner similar to that of the patients who had pneumococci in the sputum. The patient with *H. influenzae* pneumonia presented clinical and roentgenologic signs of consolidation of the right and left lower lobes. Rapid progression of infection, with increased fever, symptoms, physical findings and x-ray evidence of extension occurred during seventy-two hours of carbomycin therapy. Institution of streptomycin was followed by prompt improvement. One case of *M. pyogenes* (var. *aureus*) pneumonia was complicated by empyema from which the same organism was obtained in pure culture. The other patient with staphylococcal pneumonia had bacteremia and multiple focal abscesses of the kidney. Both are described in greater detail under *M. pyogenes* infections. No clinical or bacteriologic improvement was noted in either patient despite intensive carbomycin therapy for five days.

Acute Bronchitis

Eight patients presented fever, malaise, productive cough and leukocytosis, but no roentgenologic

evidence of pneumonitis. *D. pneumoniae* was isolated from the sputum of 2 patients, and *H. influenzae* from another. The sputum of the remaining 5 patients showed only normal throat inhabitants on culture. A prompt clinical response was observed in all cases, the temperature returning to normal within twenty-four hours of the institution of carbomycin therapy and the quantity and character of the sputum improving more gradually. *D. pneumoniae* disappeared from the sputum, but *H. influenzae* in large numbers persisted throughout therapy. Additional improvement and eradication

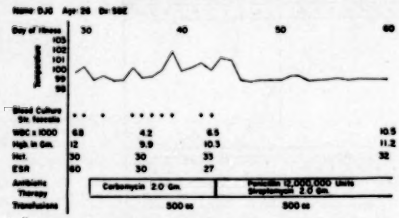

FIGURE 7. *Clinical Course of Enterococcal Endocarditis Treated with Carbomycin.*

of *H. influenzae* were accomplished after institution of bacitracin-polymixin aerosol.

Bacterial Endocarditis

Five patients presented bacterial endocarditis, 2 due to an enterococcus, 2 to nonhemolytic streptococci that were not fecal in type and 1 to *M. pyogenes* (var. *aureus*).

The 2 patients with enterococcal endocarditis were treated for periods of five and ten days. The organism of the first of these showed in vitro sensitivities as follows: penicillin, 5.0 units, terramycin, 100 microgm., bacitracin, 10.0 units, and carbomycin 0.63 microgm per cubic centimeter. Therapy with carbomycin both orally and intravenously was not followed by clinical improvement, and bacteremia persisted. Treatment with 20,000,000 units of penicillin and 2.0 gm. of streptomycin daily likewise was not followed by clinical or bacteriologic response. At autopsy a large mesenteric abscess in the lesser peritoneal sac was found in addition to bacterial endocarditis of the aortic valve. The part in therapeutic failure that the abscess played in providing a focus unavailable to antibiotic agents should probably be emphasized. The enterococcus from the other patient (Fig. 7) showed in vitro sensitivities as follows: penicillin, 10 units, streptomycin, 100 microgm., terramycin, 10 microgm., and carbomycin, 0.16 microgm. per cubic centimeter. Clinical activity and bacteremia persisted during the entire period of carbomycin therapy. Prompt and continued response followed institution of combined penicillin and streptomycin therapy for six weeks.

Of the 2 patients with subacute bacterial endocarditis due to nonhemolytic streptococci the organism of the 1 (Fig. 8) had in vitro sensitivities as follows: penicillin, 0.025 units, terramycin, 1.56 microgm. and carbomycin, 1.56 microgm. per cubic centimeter. After institution of carbomycin therapy prompt clinical response occurred although a positive blood culture was obtained on the fifth day of therapy. A satisfactory clinical course, with negative blood cultures, then ensued until the twenty-first day of therapy, when signs of sepsis again appeared and a nonhemolytic streptococcus with the in vitro sensitivities listed above was again isolated. The

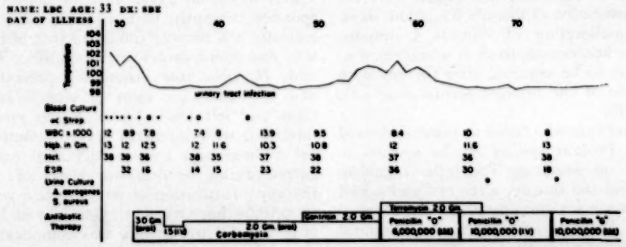

FIGURE 8. *Clinical Course of Subacute Bacterial Endocarditis Treated with Carbomycin.*

total dosage was 50 gm. Prompt clinical response, with negative blood cultures, followed therapy with 10,000,000 units of penicillin daily. Follow-up study for six weeks after discontinuance of penicillin showed this patient to be apparently cured. The nonhemolytic streptococcus of the second patient (Fig. 9) showed in vitro sensitivities as

follows: penicillin 0.39 units, terramycin, 0.39 microgm., bacitracin 0.39 microgm., and carbomycin 0.78 microgm. per cubic centimeter. Fever and positive blood cultures persisted despite 3-gm. daily doses of carbomycin by mouth. Dramatic clinical improvement and disappearance of bacteremia followed institution of 10,000,000 units of penicillin daily and persisted for more than five weeks.

Two patients with acute bacterial endocarditis due to *M. pyogenes* (var. *aureus*) are described below. Carbomycin therapy produced temporary improvement with control of bacteremia in 1 of these but failed to alter the course of the disease in the other.

M. pyogenes (*var.* aureus) *Infections*

Seven patients were treated for serious acute staphylococcal infections, and 5 died. Bacteremia was present in 4 cases. The in vitro sensitivity to carbomycin of the *M. pyogenes* in each case was within a range that could be regarded as sensitive.

Two of the 7 patients showed a satisfactory response to carbomycin therapy. The first of these was a patient with acute bacterial endocarditis due to *M. pyogenes* (var. *aureus*) with in vitro sensitivities as follows: penicillin, over 50 units, terramycin, 3.6 microgm., and carbomycin, 1.25 microgm. per cubic centimeter. Temporary clinical response, with control of bacteremia, occurred, but the patient died from cerebral embolism after five days of carbomycin therapy. The second patient had lymphatic leukemia complicated by multiple staphylococcal abscesses of the skin and a perirectal abscess. Carbomycin therapy was followed by healing of the skin lesions and improvement of the perirectal abscess. No new skin lesions appeared.

Five patients failed to show any significant response to carbomycin therapy. The first was a fifty-eight-year-old man with acute bacterial endocarditis and acute pyelonephritis. He had been treated with terramycin on two occasions, with temporary improvement. However, cessation of therapy had been followed by relapse on both occasions. Blood and urine cultures were repeatedly positive for *M. pyogenes*. The blood urea nitrogen was 64 mg. per 100 cc. at the time carbomycin therapy was instituted. Sensitivity tests were as follows: penicillin, over 10 units, terramycin, 0.625 microgm. and carbomycin, 1.25 microgm. per cubic centimeter. Sepsis and bacteremia continued despite administration of carbomycin in a daily dose of 2.0 gm. orally and 800 mg. intravenously for three days. Institution of penicillin (50,000,000 units daily by continuous intravenous drip) and terramycin (1 gm. daily intravenously) therapy was followed by return of temperature to normal and control of bacteremia. However, uremia was progressive, and the patient died after four days of the combined therapy.

The second patient was a fifty-seven-year-old man with staphylococcal pneumonia of the right lower lobe. Uremia and an infection of the genitourinary tract were also present in this patient. Blood and urine cultures were positive for *M. pyogenes*. Sensitivity studies were as follows: penicillin, over 25 units, terramycin, over 25 microgm., bacitracin, 1.56 units, and carbomycin, 5.0 microgm. per cubic centimeter. Carbomycin was administered in a daily dose of 1600 mg. intramuscularly. Serum concentrations were 10 microgm. per cubic centimeter four hours after injection and 5.0 microgm. six hours after injection on two different occasions.

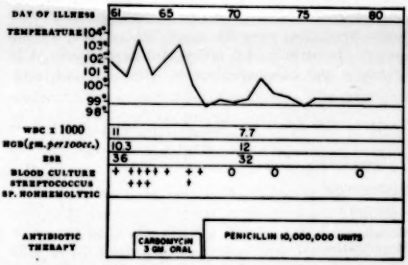

FIGURE 9. *Clinical Course of a Thirty-Eight-Year-Old Patient with Subacute Bacterial Endocarditis Treated with Carbomycin.*

The clinical picture improved during the first two days of carbomycin therapy but was followed by recurrence of fever and bacteremia. After the institution of bacitracin 50,000 units daily in divided doses, clinical improvement occurred, the temperature returned to normal, and blood cultures became negative. However, uremia became progressively worse, and the patient died. At autopsy multiple small abscesses were present in the lower lobe of the right lung and in both kidneys. *M. pyogenes* was cultured from lung and kidney.

The third patient was a thirty-two-year-old woman who was convalescing from infectious mononucleosis associated with hepatitis. A carbuncle of the face developed, and this was followed by chills, fever (maximum temperature of 104°F.) and regional lymphadenopathy. There was a history of a severe anaphylactoid-type reaction after penicillin therapy. *M. pyogenes* was isolated from the carbuncle. Blood cultures were negative. Sensitivity studies were as follows: penicillin, 0.05 units, terramycin, 25 microgm., bacitracin, 1.56 units, and carbomycin, 0.78 microgm. per cubic centimeter. Treatment with carbomycin in an oral dose of 250 mg. every six hours for three days failed to alter the acute septic course of the disease. On the third day of therapy abrupt pain in the

left upper quadrant and left lower part of the chest appeared. Physical examination revealed tenderness and muscle spasm of the left upper quadrant. Fluoroscopic examination showed fixation of the left leaf of the diaphragm. A staphylococcal metastatic lesion involving the spleen or left subdiaphragmatic space was suspected. Treatment with terramycin, 1.5 gm. intravenously each day, was followed within twenty-four hours by subsidence of fever. Over a period of several days the abdominal signs and symptoms disappeared, and the carbuncle resolved.

The fourth patient was a fifty-three-year-old man with staphylococcal pneumonia and empyema. *M. pyogenes* was predominant in the sputum and was isolated repeatedly in pure culture from the empyema fluid. Sensitivity studies were as follows: penicillin, over 25 units, terramycin, 50 microgm., bacitracin, 1.6 units, and carbomycin, 1.25 microgm. per cubic centimeter. Pencillin and terramycin had failed to influence the course of the disease. Despite 2.0 gm. of carbomycin orally and 400 mg. intrapleurally daily no clinical improvement occurred, and *M. pyogenes* continued to be present in large numbers in the sputum and empyema fluid.

TABLE 5. *Side Effects after Oral Administration of Carbomycin.*

SIDE EFFECT		NO. OF CASES
Gastrointestinal:		10
Nausea and vomiting	5	
Diarrhea	4	
Brown tongue	1	
Skin eruption		3
Mental changes		2 (?)
Total		15

The fifth patient was a thirty-eight-year-old man with atrophic rhinitis. After cortisone therapy evidence of severe sepsis associated with cough, purulent sputum, hemoptysis, multiple embolic lesions of the skin and bacteremia with *M. pyogenes* developed. This organism was also isolated from the sputum and from the skin lesions. Sensitivity studies were as follows: penicillin, 0.19 units, terramycin, 0.10 microgm., bacitracin, 1.56 units, and carbomycin, 0.78 microgm. per cubic centimeter. Treatment with each of these antibiotics failed to alter the clinical course of this disease. At autopsy multiple lung abscesses were found.

Acute Follicular Tonsillitis

Six patients had acute follicular tonsillitis. Good clinical response occurred in all, with decline of fever in twenty-four hours and subsidence of symptoms and signs over forty-eight to seventy-two hours. One patient showed persistence of beta-hemolytic streptococci during the entire period of seven days of chemotherapy. Another, from whom large numbers of *D. pneumoniae*, Type 3, were isolated in almost pure culture, showed persistence of this organism after six days of treatment. One patient had severe fusospirochetal infection of the throat, with regional lymphadenitis. After forty-eight hours of carbomycin therapy the temperature had returned to normal, marked improvement of the oral cavity had occurred, and smears were negative for fusiform bacilli and spirochetes.

Urinary-Tract Infections

Six patients presented chronic urinary infections. *Str. faecalis* was present in pure culture in 4 patients, and *M. pyogenes* (var. *aureus*) in 2. Bacteremia with *Str. faecalis* was present in 1 and obstructive uropathy existed in 5. No definite symptomatic improvement occurred in these cases. Enterococci were eradicated from the urine of 2 patients and persisted in 2. *M. pyogenes* continued to be present in the urine but disappeared temporarily after therapy with terramycin.

Amebiasis

Five patients presented amebiasis, with cysts or trophozoites of *Endamoeba histolytica*, or both, in the feces. Only 1 had bloody diarrhea, which completely disappeared within forty-eight hours of institution of carbomycin therapy. Cysts and trophozoites disappeared from the feces of all 5 patients after seventy-two hours of chemotherapy. The feces of 4 patients restudied six weeks after discontinuance of treatment were still negative for *E. histolytica*. One patient showed persistent fever and right-upper-quadrant pain and tenderness despite eradication of *E. histolytica* from the feces on carbomycin therapy. Institution of chloroquine was followed by prompt remission of fever and abdominal findings. Relapse after discontinuance of chloroquine and the presence of an enlarging right-upper-quadrant mass necessitated drainage of a large hepatic abscess, which was sterile on culture and showed no amebas by direct examination or histologically.

Toxicity and Side Effects

Of the 57 patients treated 15 manifested side effects (Table 5). Nausea, vomiting or diarrhea — or all three — appeared in 5 of the 51 patients receiving 2.0 gm. and in 4 of the 6 patients receiving 3.0 gm. daily. Three of the patients with gastrointestinal side effects after 3.0 gm. daily tolerated well a daily dose of 2.0 gm. Administration of carbomycin with food relieved the gastrointestinal symptoms in several cases. Skin eruptions appeared on the third, fifth and sixth days of chemotherapy respectively. Two patients showed a diffuse, erythematous, mottled macular rash over the thorax and abdomen that persisted during the period of continued therapy, gave no evidence of becoming severe and subsided promptly after discontinuance of the drug. The third had scleroderma and a past

history of drug sensitivity. A severe generalized, erythematous macular rash appeared on the third day of therapy and was followed by extensive desquamation in spite of prompt discontinuance of carbomycin. No other medications were being given during the time of carbomycin therapy. Disorientation, somnolence and marked lethargy appeared in 2 patients during (but were possibly unrelated to) carbomycin therapy. Both these elderly patients presented an advancing, severe pneumonic process due to *H. influenzae* that was failing to respond to carbomycin. After discontinuance of carbomycin and control of infection with streptomycin the mental aberrations disappeared, suggesting that either uncontrolled, acute infection or drug therapy was responsible for the abnormal mental reaction observed.

Complete blood counts and urinalyses biweekly, and weekly determinations of quantitative van den Bergh reaction, cephalin flocculation and thymol flocculation, alkaline phosphatase, quantitative urinary urobilinogen, blood urea nitrogen and blood sugar revealed no case of hematologic, hepatic or renal toxicity. No clinical evidence of central-nervous-system toxicity or changes in reflexes was noted.

No cases of overgrowth of *M. pyogenes* (var. *aureus*) or monilia were observed during or after carbomycin therapy. In cases of persistence of *M. pyogenes* during carbomycin therapy the carbomycin resistance did not increase. *H. influenzae* gained predominance in the sputum during carbomycin therapy of pulmonary infections in 5 cases. Two of these patients showed an acute exacerbation of pulmonary infection apparently due to this organism while they were on carbomycin. Two additional patients with acute respiratory disease showed *H. influenzae* predominant in the sputum at the time of institution of carbomycin. The failure of all these infections to respond to carbomycin casts doubt upon the usefulness of this antibiotic in infections due to *H. influenzae* in spite of the observation that some strains may be relatively sensitive in vitro.

Summary and Conclusions

Carbomycin was active in vitro against a variety of gram-positive cocci. Bactericidal activity exists but is less than that of penicillin. Relatively resistant strains of *Staphylococcus aureus* have already been observed, and resistance may be produced readily in vitro. Cross resistance with erythromycin exists to a high degree.

Carbomycin was absorbed after oral administration of 0.5-gm. doses, with production of detectable serum concentrations in two thirds of the patients. Intravenous administration produced demonstrable serum concentrations in all patients. Carbomycin appeared rapidly in the urine, with a total excretion of 0.5 to 2.5 per cent of the dose administered.

A favorable clinical response occurred in many of a variety of acute infections due to the pneumococcus and to alpha-hemolytic, beta-hemolytic and nonhemolytic streptococci. The bacteriologic results in several of these, however, were less striking than might have been expected from penicillin. The results in 5 patients with subacute bacterial endocarditis were uniformly poor. The response in staphylococcal sepsis was not striking.

Toxicity and side effects were observed in about a fourth of the patients but did not appear to be serious.

At present it is recommended that the use of this drug be limited to patients who are hypersensitive to penicillin or the newer antibiotic agents and to those who have acute infections that have been shown to be or are frequently resistant to penicillin, aureomycin and terramycin. These will consist almost entirely of staphylococcal or enterococcal infections.

If the drug is to be employed it should be started at once in the maximum tolerated dose — at least 500 mg. every six hours — and if possible supplemented initially with parenteral administration.

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HISTOPLASMOSIS IN A LIFE-LONG RESIDENT OF NEW ENGLAND*

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It is now well known that histoplasmosis *exceptionally* is a fatal disease of the reticuloendothelial system, occurring solely in the tropics or in the states bordering the Mississippi River and its larger tributaries. The vastly more common, nonfatal, localized, pulmonary and even disseminated forms have been diagnosed in widespread localities where the index of suspicion is high and proper mycologic technics are utilized.[1-3] It is the purpose of this paper to describe the first proved case of histoplasmosis from New England, in a native of Vermont who had never visited in the endemic areas mentioned above, and to stress the tendency for adrenal involvement. In addition, the difference among direct examination of specimens, primary isolates and subcultures is briefly discussed.

Case Report

K.L., a 44-year-old man, was first admitted to the Mary Hitchcock Memorial Hospital in October, 1951, because of hoarseness of 5 years' duration, recent discomfort on swallowing, and smothering feelings on lying down. His hoarseness was gradual in onset over several months. The other symptoms had developed during the past 4 months. He had been hospitalized in a sanatorium for tuberculosis for 4 months in 1924, but since that time had had no cough, sputum or hemoptysis.

Figure 1. *Organisms of* Histoplasma capsulatum *in Laryngeal Tissue Demonstrated by Acid-Fast Stain (x 1233).*

Physical examination revealed a well developed and well nourished man who looked older than his stated age. He spoke with a hoarse voice. There were dry sonorous rales in the left upper lung field.

The blood pressure was 110/88. The pulse was 96, the temperature 98.6°F., and the respirations 20.

X-ray examination of the chest showed fine, rather dense infiltration in both infraclavicular areas and in the left apex. The lower portions of the lung fields were clear.

Laryngoscopic examination demonstrated markedly thickened false vocal cords and boggy arytenoid cartilages. The posterior commissure was filled with a firm, granular mass. The middle third of the right vocal cord was thickened and covered by a keratotic surface. This same lesion was visible on the entire posterior two thirds of the left vocal cord, extending into the left ventricle. The cords moved well. Biopsies were obtained from both cords, and from the region of the left ventricle.

Pathologically, the lesion showed stratified squamous epithelium overlying a fibrous tissue stroma containing accumulations of lymphocytes, plasma cells, necrotic débris and Langhans' giant cells. Acid-fast stains disclosed no acid-fast organisms.

Figure 2. *Specimens Planted on Sabouraud's Medium.* A = *three-week-old subculture;* B = *three-week-old primary isolate.*

After a period of rest at home, the patient was admitted to the Trudeau Sanatorium, where a 2d laryngoscopic examination was reported to have shown dense, diffuse lymphocytic infiltration of the submucosa with scattered epithelioid cell tubercles, some of which showed a small area of central caseation. Cultures of 2 sputums and a bronchial washing were positive for tubercle bacilli.

The patient was started on streptomycin and P.A.S. therapy and soon thereafter was transferred to the Vermont State Sanatorium, where he stayed until May, 1952. Sputum and gastric washings were all negative for tubercle bacilli. He was relatively well until September, 1952, when his voice began to drop to a whisper. He had no recurrence of the previous dysphagia.

In October he was again admitted to Mary Hitchcock Memorial Hospital for laryngoscopy. There had been no change since the last examination. X-ray films demonstrated fibrosis in both infraclavicular areas and the left apex. Pathological

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examination of the specimen taken at laryngoscopy again revealed submucosal tissues infiltrated by lymphocytes and plasma cells, with some collections of epithelioid cells and multinucleated giant cells. However, with acid-fast stains, pale-staining, oval, eosinophilic bodies averaging 3 microns in greatest dimension, surrounded by a distinct halo, were found in the granulomatous areas. These were primarily intracellular in macrophages and giant cells (Fig. 1). These organisms were gram positive. The periodic-acid-Schiff stains were not striking in this case, the organisms showing up best with acid-fast stains. No acid-fast organisms were found. The slides from the previous biopsies were reviewed, and no organisms similar to those described were seen.

The patient was discharged after laryngoscopy and remained at home for the next 2 months. In late December he had a severe attack of nausea, vomiting and diarrhea that lasted for 3 weeks. Oliguria and the frank signs of adrenal insufficiency then developed, with weak, thready, rapid pulse, a blood pressure of 70/0, weakness and anuria, and he was again hospitalized at Mary Hitchcock Memorial Hospital. After stabilization, a Thorn eosinophil count was done. The initial count was 250 eosinophils per cubic millimeter and, after the test material was injected, the count rose to 294 eosinophils per cubic millimeter. Multiple sputums were negative for acid-fast organisms on smear and culture.

One tenth of 1 mm. of Histoplasmin (Lilly), 1:1000 solution, was injected intradermally into the flexor aspect of the right forearm. At 48 hours, an erythematous papule measuring 9 mm. developed, persisting for 1 week. The complement-fixation titer for histoplasmosis was 1:2, and the precipitin titer 1:32. Identical titers were obtained 2 weeks later.*

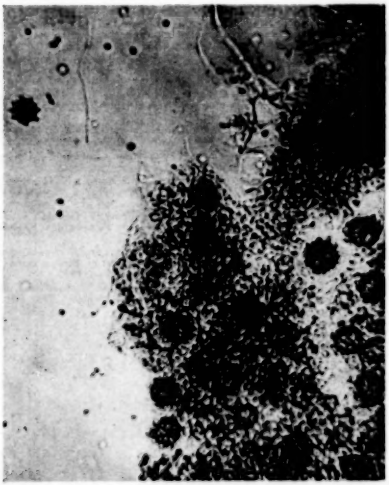

FIGURE 3. *Cultural Mount, Demonstrating Several Diagnostic Tuberculate Chlamydospores.*

Specimens for culture were obtained from sputum, gastric washings, blood and biopsy tissue removed from the larynx. Out of 40 cultures taken, only 1 was positive for *H. capsulatum*. This specimen came from the laryngeal tissue, and was planted on Sabouraud's medium without the addition of antibiotics. The first growth was noted at 2 weeks, when a subculture was performed on a Sabouraud agar slant. At 5 weeks the primary isolate remained a small, brownish, granular colony, whereas the 3-week-old subculture produced a large, cottony growth (Fig. 2). Cultural mounts demonstrated the diagnostic tuberculate chlamydospores (Fig. 3 and 4).

*Performed by Dr. S. Salvin, Rocky Mountain Laboratory, United States Public Health Service, Hamilton, Montana.

Discussion

This case can be definitely classified as localized histoplasmosis of the larynx, with a strong possibility of pulmonary histoplasmosis. Repeated cultures and animal pathogenicity studies were negative for *Mycobacterium tuberculosis*. However, there was a history of three positive cultures for this organism in the past, and pulmonary tuberculosis must still be considered in the differential diagnosis. Histoplasmosis has been associated with tuberculosis in well over a dozen cases.[4]

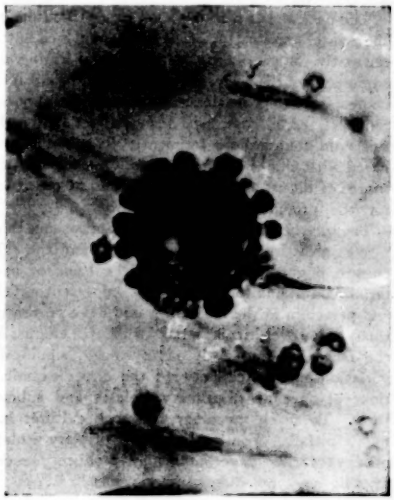

FIGURE 4. *Enlarged Tuberculate Chlamydospore.*

It is also likely that dissemination of histoplasmosis took place with adrenal involvement. In a review of 78 cases of histoplasmosis Parsons and Zarafonetis[5] found the adrenal glands to be the third most common organ involved histologically. Massive adrenal destruction from histoplasmosis has been noted on several occasions,[6] producing clinically all the signs and symptoms of adrenal insufficiency.

Pinkerton and Iverson[7] report 3 cases of histoplasmosis that were originally misdiagnosed as sarcoidosis. The cause of death in every case was bilateral mycotic caseation of the adrenal glands. In the caseous material, periodic-acid-Schiff stains demonstrated a profusion of *H. capsulatum* organisms that could not be identified in sections stained in the routine manner. These studies indicate that

some of those cases with the diagnosis of sarcoidosis may be due to histoplasmosis.

The patient described above has spent his entire life in New Hampshire and Vermont except for the following occasional excursions: he drove to Boston on four or five occasions, and once motored to New York City for an overnight trip; in the winter of 1952, he traveled by automobile to the Trudeau Sanatorium in New York, where he was a bed patient for about six weeks; he then returned to Vermont by car.

The patient has worked in a Vermont mill during the winter months, and has been employed intermittently for years on a Vermont farm during the summer months. He performed the usual farm chores, including the cleaning out of chicken houses. Since *H. capsulatum* has been isolated from the soil[8] and found more frequently in soil contaminated with chicken excreta,[9] this is the most likely source of the infection. (This soil is to be examined for the presence of *H. capsulatum*.)

The marked difference in the appearance and rate of growth of the primary isolate and the subculture might be explained on the basis of bacterial contamination. (The use of streptomycin and penicillin in the medium would have prevented this.) However, it is worth while to emphasize the fact that frequently in mycology, significant variations are noted between the direct examinations of specimens, primary isolates and subcultures. To teach mycology by stock cultures has many pitfalls. For example, the primary isolate of *Cryptococcus neoformans* may produce pseudomycelia and no diagnostic capsules.[10, 11]

Direct examination of sputum for *Nocardia asteroides* may demonstrate bacilli with a definite acid fastness indistinguishable from that of *M. tuberculosis*. The organism may become partially acid fast in the primary culture and nonacid fast on repeated subcultures.[12]

Summary

The first case of proved histoplasmosis from New England is described. It is believed that the disease was acquired in Vermont. Adrenal involvement in histoplasmosis is stressed, as well as the cultural differences between primary isolates and subcultures.

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ACUTE RENAL INSUFFICIENCY DUE TO BICHLORIDE OF MERCURY*

Observations on Gastrointestinal Hemorrhage and BAL Therapy

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THE clinical management of the oliguric patient still represents a difficult and challenging problem despite the advances in knowledge of the underlying pathologic physiology of acute renal insufficiency. The difficulties stem largely from the fundamental nature of the syndrome and the course it pursues, both of which render the patient particularly susceptible to many grave complications. The case described below illustrates a number of the complications, including massive gastrointestinal hemorrhage, and the important problem of British anti-lewisite (BAL) therapy in the oliguric patient is discussed in some detail.

CASE REPORT

M. H. (G. U. H. 28,266), a 28-year-old married woman, swallowed 4 tablets (2 gm.) of bichloride of mercury on December 26, 1949. When admitted to Gallinger Municipal Hospital, Washington, D. C., 2½ hours later, she was in mild shock. A bloody diarrhea began shortly thereafter, and she complained of diffuse abdominal tenderness and a sensation of burning in the epigastrium. The past history failed to disclose any kidney or heart disease, and a review of the systems was not contributory. On catheterization, 240 cc. of brown, guaiac-positive urine was obtained. There was a submucosal hemorrhage on the left buccal region but no other evidence of glossitis. The fecal material and vomitus both gave a positive test for blood. The shock-like state cleared after institution of oxygen and parenteral fluid therapy. BAL antidote therapy was not started until 3 hours after ingestion of the mercury. Each injection was followed by vomiting and a transient rise in blood pressure.

The patient was transferred to Georgetown University Hospital on the 2d day. A routine form of conservative fluid therapy was begun. Table 1 shows some of the intake and output measurements as well as the salient laboratory determinations. BAL therapy was continued although the dosage was changed and on 2 occasions it was temporarily stopped (Table 2). The only reactions encountered were nausea and a burning sensation of the face, throat and hands. The administration of ephedrine sulfate 30 minutes before each injection of BAL did not prevent or relieve these reactions.

Hemodialysis was performed on the 9th day because of persistent oliguria, early electrocardiographic signs of potassium intoxication and moderately severe acidosis. The chemical changes effected by a 4-hour period of hemodialysis are recorded in Table 1.

Since admission to the hospital there had been a continuous fall in the hematocrit values, and therefore 400 cc. of whole blood was administered during the dialysis. On termination of the procedure the blood contained within the cellophane loops of the machine was also given. The rate at which this blood was delivered proved to be excessively rapid and within ½ hour severe pulmonary edema had developed. Treatment was begun immediately, consisting of positive-pressure oxygen, bloodless phlebotomy, rapid digitalization, morphine, aminophylline and further restriction of fluids. Her condition remained unchanged during the following 30 hours; 500 cc. of blood was then removed, and by the 11th day the pulmonary edema had improved. Between the termination of the dialysis and the morning of that day, the hematocrit readings had been fairly consistent. Serial

TABLE 1. *Results of Blood Chemical and Hematocrit Determinations, Body Weights and Intake and Output Measurements.*

DAY	BLOOD UREA NITROGEN mg./100 cc.	CARBON DIOXIDE milli-equiv./liter	CHLORIDE milli-equiv./liter	SODIUM milli-equiv./liter	POTASSIUM milli-equiv./liter	HEMATOCRIT %	WEIGHT kg.	INTAKE cc./day	OUTPUT URINE cc./day	OUTPUT STOOL cc./day	OUTPUT VOMITUS cc./day	OUTPUT TOTAL cc./day
1	10	18	82.0					4050	470	150	720	1340
2						44	51.6	1550	79	160	150	389
3	48	18	85.5	128.0	3.6		51.0	1255	35	115	65	215
4	89	14	83.0	127.0	4.3		50.0	1200	185	10		195
5		16	71.0	126.0	4.6		51.1	1100	258	165	55	478
6	160	14	73.7	123.9	6.9	36	50.9	1000	260		60	320
9*	160	11	71.0	126.1	7.7	26						
	47	18	99.9	138.0	5.1	28			190	250		440
11	93	14	100.9	145.7	7.2	33		805	165	110		275
13				138.0	7.8	23		820	368	90	114	572
14	229	11	96.6	141.0	8.2	18		600	720	250		970
15	265	11	94.3	140.0	7.6	17		1100	1320	30		1350
16	294	9	100.0	147.8	8.3	20		2100	1800			1800
20						25		4625	1890	800		2690
21	322	15	97.4	147.8	5.1	33		3300	2650	300		2950
23	298	20	101.6	148.9	4.4	42		3340	2620			2620
25	266	19	99.1	146.8	2.6	40		10,700	3510	2520		6030
26	196	21	105.0	147.8	3.4	25		8100	4420	1100		5520
27						34		3000	5285	425	150	5860
28	110	26	105.0	150.0	2.7	46		2080	2850	380		3230
30	67	29	107.6	156.5	3.2	45	38.6	2010	1380		300	1680
39	18	24	107.7			41		2530	1900			1900

*Values before and after a 4-hour dialysis on the artificial kidney.

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The opinions expressed and the assertions made are the private ones of the authors, or the senior author, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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determinations performed during that and the succeeding day again revealed a progressive fall.

Diuresis occurred on the 13th day. Three days later the blood urea nitrogen was 294 mg. per 100 cc., and the carbon dioxide 9.0 milliequiv. per liter; a friction rub was audible, and the chest and face were covered by a thick uremic frost. The patient seemed moribund, but a repeat dialysis was not attempted because the gastrointestinal bleeding had increased in severity.

The bleeding had continued despite fresh blood transfusions, and on the 20th day blood began to ooze continuously from the rectum. A state of mild shock developed that was soon corrected by additional transfusions. Concurrently, thrombin, gelfoam, milk and Amphojel were administered through a Levin tube, and a mixture of gelfoam and thrombin was instilled into the sigmoid colon. These procedures were repeated 2 or 3 times,

TABLE 2. *Data on BAL Therapy.*

DAY	DOSAGE	SERUM CONCENTRATION*		URINE VOLUME
		TOTAL	REDUCED	
	mg./day	mg./100 cc.	mg./100 cc.	cc./day
1	800			470
2	1600			79
3	600	9.0		35
4	600	3.9†		75
5	200	4.3		185
6	200	2.3‡		189
7	400	11.6		258
8	400	11.5		260
9	200	13.6§	3.3	190
		5.4¶		
10	0	7.4		164
11	0			165
12	100			244
13	150			368
14	150	1.3		720
15	150			1320
16	200	16.7	4.1	1800
17	0	20.8	5.1	2400

*All serum concentrations performed on blood specimens drawn at 8 a.m.

†No BAL administered during a 16-hour period on day 3.

‡No BAL administered during preceding 15 hours.

§Serum concentration immediately before dialysis.

¶Serum concentration immediately after 4-hour dialysis.

each day. The dosages of BAL and penicillin were increased, and streptomycin started. On the following day pyribenzamine, vitamin C and rutin were added to the hemostatic agents being given. Dr. Charles Rath saw the patient and concurred with the diagnosis of uremic gastroenteritis, and in addition offered the opinion that it was the sole cause of the bleeding.

Accordingly, BAL was discontinued and intravenous injection of aureomycin begun. Two days later the administration of ACTH was begun in the hope that it might exert a beneficial effect on the persistent bleeding.

On the 25th day, fresh red blood, bearing a pungent, ammoniacal odor, gushed from the rectum, and a profound state of shock supervened. The greatest portion of the total blood expelled at this time was collected (2520 cc.). Despite the administration of 4200 cc. of blood that day the hematocrit fell from 40 to 25 per cent. Some of this decrease was due to excessive hydration, for 6500 cc. of fluid was given intravenously in addition to the blood. Fluids were forced in an attempt to expand the extracellular fluid compartment rapidly and thereby to lower the blood urea nitrogen by dilution. Potassium chloride was added to a portion of these fluids because of a coexisting hypokaliemia. By the following day the blood urea nitrogen had fallen 70 mg. per 100 cc., the rectal bleeding had slackened, and the patient was responsive.

Fluids continued to be forced, and a total of 8100 cc., including 3600 cc. of blood, was administered on that day. By the 27th day there was extensive periorbital edema, but no rales were audible and the heart rate had slowed. Within 72 hours the blood urea nitrogen had fallen to 156 mg. per 100 cc., and the rectal bleeding brought under control. The ACTH, rutin and pyribenzamine were discontinued. Aureomycin was continued by the oral route, and the diet was supplemented with an additional 2 gm. of potassium chloride daily.

Between the 8th and the 30th day the patient had lost 12.3 kg. (27.1 lb.). This amount, which was equal to 25 per cent of her normal body weight, indicates the intensity of the catabolic reaction sustained during this 3-week period. It does not represent the maximal weight loss, for she was well hydrated and had been eating for 4 days before this weighing. Her appetite was excellent, and a soft, high-protein, high-calorie diet was well tolerated.

Serial sigmoidoscopic examinations performed by Dr. Irving Brick revealed a progressive healing of the colitis. The patient was discharged from the hospital 56 days after ingestion of the mercury. Follow-up examinations during the next 3 months revealed a continuous gain in weight and no significant gastrointestinal or genitourinary abnormalities other than a low specific gravity of the urine.

DISCUSSION

Of the many problems that this patient presented, only those pertaining to massive gastrointestinal hemorrhage and BAL therapy are discussed.

Gastrointestinal Hemorrhage

The gastroenteritis was of the gravest severity. Although probably initiated by the bichloride of mercury, it became progressively worse as the uremia increased in severity and duration. Since the moiety of mercury that continues to be excreted by the colon is capable of causing a colitis in particularly sensitive persons, BAL therapy was continued for a longer period than usual. It, as well as fresh blood transfusions, aureomycin, vitamin K, ACTH, pyribenzamine, rutin, ascorbic acid, thrombin and gelfoam, had no clinically obvious effect on the bleeding, nor did they significantly alter the results of the hematologic studies. These studies included repeated red-cell and white-cell, differential, reticulocyte and platelet counts, and bleeding, clotting, prothrombin and plasma recalcification times, as well as serum bilirubin and various blood agglutination studies.

The exact cause of bleeding in uremic gastroenteritis remains unknown, but three factors are considered to be of importance: the excretion of urea into the gastrointestinal tract, the action of intestinal bacteria and the generalized bleeding tendency associated with the uremic syndrome.[1-4] One hypothesis states that the bleeding results from the excretion of urea into the gastrointestinal tract, where it is hydrolyzed by the intestinal bacteria into ammonia and carbonic acid, the resulting ammonium carbonate directly damaging the mucosa. In view of the pungent ammoniacal odor and strongly positive qualitative test for ammonia given by the fecal material, this appeared to be a plausible explanation. At first large amounts of aureomycin were given in an attempt to sterilize the gastrointestinal tract and thereby interrupt the cycle. It soon became apparent that a more important factor was the reabsorption of blood from the lumen of the gut, which elevated the blood urea nitrogen to disproportionately high concentrations and as a consequence caused more urea to be excreted by the intestine, thereby aggravating the bleeding. In the presence of severe hemorrhage and impaired renal function the only means available for rapidly lowering the blood urea ni-

trogen and thereby interrupting the cycle was the regimen of forced dilution therapy.[5] Excessive quantities of fluid were administered on the 25th and 26th days, and although edema was present on the 27th day, the blood urea nitrogen had been drastically lowered and the hemorrhage brought under control. Dilution alone did not account for the lowering of the blood urea nitrogen, for as fluid was forced the urine volume fortuitously increased and 84 gm. of total nitrogen was excreted in seventy-two hours. The clinical improvement within the same period was dramatic. Apparently, statements concerning the benignity of elevated blood urea, per se, do not apply to the uremic patient with gastrointestinal hemorrhage.

BAL Therapy

Although BAL (2-3 dimercaptopropanol) has proved to be a highly effective antidote in bichloride of mercury poisoning, important problems concerning its clinical use remain in need of clarification. Certain observations that illustrate some of these problems have been made on this patient and 3 others who had also ingested bichloride of mercury and were given BAL.

One of the patients, H. C. (G. U. H. 24948), seen six months earlier, was also a young woman who became anuric an hour after ingesting bichloride of mercury. BAL was administered within two hours of ingestion and continued regularly thenceforth, except for a brief interruption. The patient remained almost completely anuric until death nine days later from progressive liver failure, severe gastrointestinal hemorrhage and circulatory collapse. During the survival period she complained of muscular weakness, a sensation of constriction in the throat, paresthesias, nausea and vomiting. Shortly before death the serum BAL concentration was 53 mg. per 100 cc.* Fatal reactions of a similar type have been described in laboratory animals given large amounts of BAL.[7]

Two additional patients, A. E. (G. U. H. 25787) and N. S. (G. U. H. 26147), both women, were treated with BAL in dosages that exceeded 3 mg. per kilogram of body weight. In both cases treatment was instituted within an hour of ingestion of the mercury, and liberal amounts of fluids were administered under careful supervision. Neither patient became oliguric, and except for one episode in patient N. S., in which serum obtained within an hour of the injection of BAL contained a concentration of 11 mg. per 100 cc., all blood specimens failed to reveal a detectable amount. The urine of this patient contained concentrations ranging between 163 and 394 mg. per 100 cc. of the oxidized form of BAL.

Table 2 presents the data in the case reported above during BAL therapy. It will be noted that although treatment was begun promptly a larger amount should have been given during the first twelve to twenty-four hours. Between the third and the sixth day there was a slow fall in serum concentration despite the administration of smaller daily dosages and the complete cessation of therapy for one period of fifteen and one of sixteen hours. Between the sixth and the ninth day there was a cumulative rise in serum concentration as the dosage was increased. The serum level was lowered 60 per cent during a four-hour run on the artificial kidney, demonstrating that BAL is readily dialyzable. The methods employed for the quantitative determination of BAL and mercury were not sensitive enough to measure the amounts contained in the dialysate because of the large dilution. Between the twelfth and the seventeenth day cumulatively high concentrations again occurred despite the administration of somewhat smaller doses and the onset of diuresis. One explanation for this may be that BAL was being handled differently by the body at this time or that some of the drug previously given was then being delivered back into the circulation. Another important factor was that during this period the uremia was at its height, which raises the possibility that the number of sulfhydryl-bearing compounds present in the serum was greatly in excess of normal. The high concentrations obtained may therefore have been partially the result of methodologic error. However, when this procedure was employed in the analyses of serum from other patients with uremia but not receiving BAL, it failed to reveal any detectable blank values.

Studies with radioactively tagged BAL have demonstrated that 80 per cent of an administered dose is excreted by the kidney within twenty-four hours.[7] A small amount is also normally eliminated by the lungs. In view of the predominant renal excretion and known toxicity of the drug, the problem arises whether it should be continued in the patient in whom acute renal insufficiency develops and, if so, in what dosage. The answer to this question is complicated by the fact that although the BAL-mercury complex is a stable one in vitro, little is known of the factors that govern its stability in vivo.

The data collected from these 4 patients indicate that no accumulation of the drug occurs unless oliguria supervenes and that under such circumstances either a cumulative rise in serum concentration accompanies further administration of the drug or, if it is discontinued, a slow decremental decline in concentration results. The possibilities

*The serum BAL concentrations were determined in the following indirect manner. The sulfhydryl groups in the plasma or serum were measured by the Hess[4] method for determining glutathione content, pure BAL being employed to standardize the method. Since glutathione is contained only in the erythrocytes the sulfhydryl group content serves, under these circumstances, as a measure of the administered BAL. The method is capable of measuring both the reduced (active) and total BAL, the difference between the two representing oxidized BAL. The method does not measure the BAL-mercury complex. Although both ascorbic acid and cysteine react with iodine, their concentrations in the plasma are not ordinarily sufficient to introduce an error of significant magnitude. In the light of these facts and the presence of uremia, the results were interpreted in terms of directional changes and not on a basis of absolute values.

exist under such conditions that a larger than normal amount of BAL is eliminated by the lungs and that some is excreted by the intestine. Although no studies were performed to test these possibilities the cumulative rise in serum concentration of BAL that occurred in the case reported above suggests that, at best, small and insufficient amounts were eliminated by these routes.

On the basis of the limited amount of data available no conclusive answer can be given to the problem of continuing therapy after oliguria is established. Our present policy is to discontinue therapy if the patient's condition permits. If the advisability of such a course seems questionable, the drug is continued but the dosage is reduced to 75 to 100 mg. a day. This amount is given in two or three divided doses, and the patient is closely observed. The drug is immediately discontinued if any toxic reactions appear.

It should be re-emphasized that BAL must be given as early as possible. The interval between the ingestion of mercury and the institution of therapy should be measured in minutes rather than hours. The plan of BAL therapy described by Longcope and his associates[8] is the one most frequently employed. Initially, an intramuscular injection of 300 mg. is given. This is followed within the first twelve hours by two or even three further injections of 150 mg. each. During the next twelve hours one or two additional injections, of 150 mg. each, are given. Depending on the patient's condition, therapy employing 150 to 300 mg. a day may be continued over the subsequent day or two.

BAL therapy alone is not the only consideration in the initial phase of treatment. Equal or even greater emphasis must be placed on the prevention of circulatory collapse. A bladder catheter should be inserted, and fluids given in liberal amounts as long as adequate urine volumes are passed. The combination of adequate amounts of BAL, given early, and the administration of sufficient quantities of fluid should reduce the occurrence of renal failure to a minimum.

Summary and Conclusions

A case in which acute renal insufficiency followed the ingestion of bichloride of mercury is presented. During the oliguric phase a progressive acidosis and uremia developed, and early signs of potassium intoxication appeared. Hemodialysis was performed on the ninth day, and pulmonary edema developed upon termination of the procedure.

Gastrointestinal bleeding which had been continuous since admission, resisted all treatment and eventually became massive. A dramatic decrease in bleeding and clinical improvement occurred when the blood urea nitrogen was lowered by a forced dilution regimen.

Data were collected indicating that in patients with bichloride of mercury poisoning BAL therapy should be discontinued if acute renal insufficiency develops. If conditions are such that it must be continued, the drug should be given in smaller doses, and the patient carefully observed for signs of intoxication. BAL is readily dialyzable.

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MEDICAL PROGRESS

THE EFFECT OF AGING OF POPULATION ON GENERAL HEALTH PROBLEMS*

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PEOPLE the world over are living for a longer time than they used to do. This is changing the age composition of society. It is altering the relative size of the many problems that society faces, and it creates new problems. Of these facts and the desirability of studying their significance and the best method of handling them there is a growing appreciation among leaders in business, labor and public administration. The interest of the medical profession in the health aspects is shown by the expanding work of organizations devoted to geriatrics and gerontology.

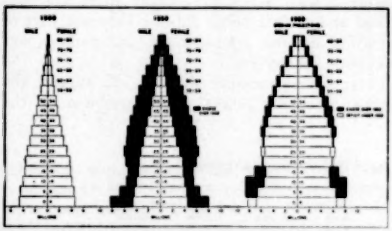

FIGURE 1. *Population of the United States by Age and Sex in 1900 and 1950, with an Estimation for 1960 (Constructed by Dr. Henry D. Sheldon and Reproduced through the Courtesy of the Bureau of the Census, United States Department of Commerce).*

Too many physicians, however, still equate old age with failing health, and consider the classic lectures of Dr. Alfred Worcester[1] on the care of the aged, the dying and the dead to be the sum and substance of geriatrics. Too many assume that the problems of old people are either insoluble or not sufficiently important to warrant thorough study. The more disagreeable features of old age have been thrust into view by nurses and social workers, who have been forced to cope with them and who have clamored the loudest for information and guidance. But all old people are not aged, nor are they always dying. More young and middle-aged people die than old ones. There is far more to the last third of life than the bearing of infirmities and the contemplation of death. It is the purpose of this paper to outline the health problems of aging people, to propose methods by which they can be attacked, and to suggest that research in this area can be of scientific as well as social interest.

A brief citation of statistics will reveal several points of clinical interest. Three per cent of the population of the United States were 65 years of age or more in 1870; in 1950 the figure was 8 per cent. Figure 1, constructed by Dr. Henry D. Sheldon chief of the Demographic Section of the United States Bureau of the Census and displayed to the American Gerontological Society in September 1952, demonstrates the changes that took place in the age structure of American society by pentads in the first half of this century. The chart is based on figures in Table 1, which is translated into percentages in Table 2. For comparison, Table 3 shows the proportion of the population over the age of 50 in England, France, Germany and Japan.

TABLE 1. *Population of the United States, by Age and Sex (1900, 1950 and 1960).*

AGE	1900*		1950†		1960‡	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
yr.	thousands	thousands	thousands	thousands	thousands	thousands
Under 5	4649	4546	8237	7927	6806	6539
5 to 9	4494	4403	6715	6485	8531	8191
10 to 14	4096	4005	5661	5459	8547	8181
15 to 19	3763	3813	5394	5306	7083	6824
20 to 24	3637	3718	5775	5876	5846	5730
25 to 29	3334	3212	6047	6270	5440	5464
30 to 34	2910	2660	5683	5893	5806	5983
35 to 39	2625	2353	5545	5729	6045	6308
40 to 44	2263	1995	5083	5134	5654	5919
45 to 49	1844	1620	4531	4544	5394	5675
50 to 54	1570	1381	4130	4144	4796	5024
55 to 59	1149	1068	3631	3605	4061	4345
60 to 64	920	876	3038	3022	3457	3819
65 to 69	670	637	2425	2578	2746	3125
70 to 74	451	435	1629	1783	1989	2364
75 to 79	262	259	1008	1170	1335	1740
80 to 84	123	130	499	601	701	946
85 and over	54	68	235	341	310	452

*Adjusted for "age not reported."

†Population, including armed forces overseas, based on preliminary 1950 data.

‡Medium projections, including armed forces overseas, consistent with P 25, No. 58 (courtesy of Dr. Henry D. Sheldon, chief, Demographic Statistics Section, Population and Housing Division, Bureau of the Census, Washington, D. C.; similar figures are available in a leaflet issued by the U. S. Department of Commerce, Series P. C. — 14, No. 5, October 31, 1952).

Where people live by the methods of Western civilization there has been an increase in old people in the last century, and the increase progresses at an accelerating rate. All ages have grown greatly in numbers, but the greatest relative growth has been in the middle and later years. Extrapolations for 1960 suggest further growth, even possibly

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decreased ratios for children and young adults. The chief reason for this trend seems to be the steady decline in mortality rates. Migration is not a factor the world over; in the United States it has been small for the last thirty years. The other factor that operates to change the composition of a country's population is the birth rate, which has both long-term and short-term effects. When it is high, there is a shift to the left of the current age groups; when it is lower, the wave of the generation of great fertility travels to the right and ultimately increases the aged groups. The official estimates of the numbers of people over 65 years of age to be found in 1940 and 1950 have proved considerably lower than the census has shown, perhaps partly because they are the survivors of a time when many children were born. If so, the present increased birth rate will produce many elderly persons in the twenty-first century.

TABLE 2. *Percentage of Men and Women in Various Age Groups in the United States (1900, 1950 and 1960).**

Age	1900		1950		1960	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
yr.						
All groups:						
Up to 19	43.8	45.1	34.6	33.1	36.7	34.3
20–24	38.1	37.4	37.4	38.1	34.1	33.9
45–54	8.7	8.1	11.5	11.4	12.1	12.4
55–64	5.3	5.2	8.8	8.7	8.8	9.4
65+	4.1	4.1	7.7	8.5	8.3	9.9
Adults only:						
20–44	67.7	68.3	57.1	57.0	53.7	51.6
45–54	15.8	14.7	17.5	17.1	19.0	18.8
55–64	9.4	9.5	13.5	13.1	14.0	14.4
65+	7.1	7.4	11.7	12.7	13.2	15.1

*Derived from Table 1.

The very old are a small minority that is not increasing very much. But the aging are a larger minority and are increasing rapidly; to them should be added all those who face the problems of aging in their middle years: the women whose husbands die and whose children marry and move away, the men who cannot get jobs where they will contribute too shortly to a company pension scheme and those whom persistent disablement makes dependent. It is more realistic to conclude that not 8 but perhaps 20 per cent of the population, or 25 per cent of voting citizens, are immediately concerned with being old. Many more are concerned about their being old, for they are part of us — they are our grandparents, our parents, our neighbors, ourselves.

These figures measure the size and suggest the complexity of the general health problems of the

TABLE 3. *Persons of Middle and Later Age in 1950 in Selected Countries.*

Age	England		France		Germany		Japan	
	MEN ×10⁶	WOMEN ×10⁶	MEN ×10⁶	WOMEN ×10⁶	MEN ×10⁶	WOMEN ×10⁶	MEN ×10⁶	WOMEN ×10⁶
yr.								
50–54	1.29	1.48	1.31	1.44	1.4	1.7	1.72	1.67
55–59	1.09	1.32	0.95	1.3	1.07	1.44	1.37	1.37
60–64	0.95	1.19	0.85	1.18	0.94	1.20	1.11	1.20
65–69	0.78	1.03	0.73	1.05	0.79	0.97	0.80	0.97
70–74	0.60	0.81	0.59	0.86	0.63	0.75	0.93	1.40
75+	0.61	0.96	0.63	1.08	0.56	0.70	0.015	0.017
Total	21.17	22.66	20.20	21.75	22.34	25.33	40.79	42.41
Per cent +65	9.4	12.3	9.6	13.7	8.8	9.5	4.2	5.6

*Adapted from Epidemiological and Vital Statistics Report, World Health Organization, Geneva, V pp. 562-563, September–October 1952.

The decline in mortality rates has been spectacular — an average of 1 per cent a year for the first half of this century in the United States (Table 4). The greatest number of lives saved are in children and young adults, but more and more old people are putting off the business of dying. This is well shown in Table 4. Many improvements have contributed to the better health of the nation that these figures measure, and not the least of them have been in the field of medicine. For example, cancer of the respiratory tract now threatens to outrank tuberculosis and pneumonia[3] — two prominent enemies whose submission is directly due to advances in roentgenography, pharmacotherapy and surgery.

aging. Although it is essential to study them by the scientific method of divide and conquer, it is also imperative that all studies be based on understanding the intimate and continuing relation between the old and those who will be old. Too many reports now foster the callous attitude of some

TABLE 4. *Decreases in Mortality Rates in the United States (1900–1948).**

Age	Decreases			Actual Lives Saved		
	MEN	WOMEN	BOTH SEXES	MEN	WOMEN	BOTH SEXES
yr.	%	%	%	thousands	thousands	thousands
All ages	45	56	50	676.3	783.5	1,459.8
14 and under	82	84		381.0	323.6	
15–34	70	81		111.6	132.8	
35–54	40	59		96.2	131.9	
55–74	14	37		55.3	140.3	
75+	14	21		32.1	54.9	

*Adapted from Kannisto and Pascua.[3]

people toward other people's old age — the attitude that regarded Old Age and Survivor's Insurance and Old Age Assistance laws as a means of getting rid of old workers, the attitude expressed by a hospital administrator that old people serve no sociologic function, the attitude, unfortunately attributed to Osler,[4] that because inventions and original contributions are rarely made by men over the age of forty there are no contributions of comparable merit made by middle-aged and aged men. The challenge to geriatrics is, What must be bad, what can be good?

Physicians are now in a position to answer in some degree the common question, "At your age, what can you expect?" The average expectancy of life has risen from just over 35 years in the time of the Revolutionary War to nearly 50 years at the turn of this century and to 68 years in 1952. Life-expectancy tables have been developed that show, for every year of attained age, how many years other people who have attained that age have lived on the average under that particular set of mortality rates. How they are developed is explained in a recent book by Dublin.[6] They are available in Government census reports.

In 1940 a person in the United States who had reached the age of 60 years could expect to live, on the average, 16.57 more years (Table 5). One who had reached 65 could expect to live 13.4 more years; at 70, one could look forward to 10.53 years; at 75, to 8.06 years; at 80, to 6.07 years; at 85, to 4.56 years; at 90, to 3.47 years; and even at 100 to 2.21 years. Women in early old age have an advantage of two years over men, but they lose it in late old age. Negroes in early old age have a shorter expectancy than whites, but very old Negroes tend to outlive very old whites. These figures doubtless will show increases in the 1950 census analyses because mortality rates have fallen.

Life in retirement from occupation has increased. Mr. Ewan Clague[9] expresses it as follows:

> In 1900, a white male aged 40 had an average life expectancy of slightly under 28 years, or to age 67.7; he could expect, on the average, to remain in the labor force for 24.5 years, or to age 64.5. He could anticipate, therefore, slightly over 3 years in retirement. — By 1940, the 40-year-old-white male could expect to live for an additional 30 years, or to age 70. His working-life expectancy had declined slightly, however, so that he could anticipate nearly 6 years in retirement. — For the future, a continuing widening of this gap between the total life span and the working life span seems likely.

The physician performs a useful service when he discusses with his aging patient the probable duration of his life, if it is based on these tables rather than on an attitude engendered by a current situation. It has been remarked that there is only one fatal illness — the last one. It is often mercifully short. All others clear up or make adjustments. There are emotional hazards in reaching one's fiftieth and sixtieth birthdays that can produce unfortunate changes in behavior and physical fitness. Literal acceptance of the Biblical remark that the years of man are threescore and ten makes the septuagenarian feel that he is living on "borrowed time." The life-expectancy tables include those who die tomorrow and those who fade away. If the physician finds his patient reasonably sound and consults the tables, the years ahead are surprisingly many. Two good ends are then accomplished. The physician is led to accept the patient as a going concern — or rather as a continuing, not going, organism. His zeal for caring thoroughly for presenting troubles is stimulated, and programs for the management of all other factors affecting health become worth while. And the patient is encouraged to settle down to behave as a permanent resident and not as a spectator on call. He finds that he must make long-range plans for his capacities and his economic resources. He finds confidence and value in putting forth more effort.

The health problems of the aged that are the particular responsibility of the medical profession can be described under the headings of acute infections, pharmacotherapy, surgery and chronic diseases. The attitude is maintained that there are no diseases of old age; there are only diseases in old people. Information may at some time be dis-

TABLE 5. *Life Expectancy of Aging United States Population by Pentads.*[a]

YEARS	LIFE EXPECTANCY FOR TOTAL U. S. POPULATION	LIFE EXPECTANCY FOR WHITE RACE		LIFE EXPECTANCY FOR NEGRO RACE		LIFE EXPECTANCY FOR OTHER RACES	
		MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
	yr.	yr.	yr.	yr.	yr.	yr.	yr.
60	16.57	15.68	17.72	14.48	16.54	15.36	17.62
65	13.40	12.64	14.22	12.64	14.36	12.57	14.65
70	10.53	9.92	11.08	10.53	12.24	10.06	11.93
75	8.06	7.58	8.40	8.53	10.19	7.92	9.51
80	6.07	5.70	6.25	6.86	8.36	6.26	7.55
85	4.56	4.26	4.61	5.57	6.72	4.83	5.70
90	3.47	3.22	3.43	4.45	5.23	3.52	3.92
95	2.73	2.51	2.61	3.39	3.94	2.42	2.46
100	2.21	2.04	2.04	2.46	2.89	1.56	1.42

[a]Adapted from U. S. Life Tables and Actuarial Tables, Sixteenth Census of United States, 1940. Washington: Government Printing Office, 1946.

covered that there are certain alterations of clinical importance that are due wholly to the accumulation of years of living. Reviews of work toward such data are to be found in the first six chapters of Cowdry's *Problems of Ageing*[7] and in the second and third chapters of *Geriatric Medicine*.[8] But, as of today, the practicing physician acts on the assumptions that inevitable death always has pathologic causes and disabilities are produced by pathologic agents. Since detailed clinical studies of the behavior of illnesses in old people are scarce, much weight is given to a superficial survey of nearly 8000 persons over 60 in a hospital.[9]

All varieties of acute infectious diseases occur in old people. As far as I am aware, they behave in routine fashion, exceptions being matched by unusual cases in younger groups. Differences in incidence are attributed to immunity conferred by a previous attack or to infrequent exposure to the causal agents. Infections due to the pneumococcus and streptococcus, once a chief cause of death in old age, came under control with sulfonamides and antibiotics. Many of the younger practitioners have not seen patients with the textbook picture of lobar pneumonia or erysipelas; they have no conception of the battles that were waged with them. As recently as fifteen years ago pneumonia meant four weeks in a hospital and many weeks of convalescence at home; now the fight is won in two or three days and the previous level of health returns immediately. I have the impression that antibiotics are not made less effective by age, though I have no statistics to bear it out.

Infections of the upper respiratory tract believed to be due to a virus are far more serious threats to the health and life of old people than is realized. They are often neglected by patients. Only the extreme forms are sent to specialists and hospitals; the general practitioners, who see the great majority of the cases, find inadequate descriptions in textbooks. Antibiotic agents have not helped greatly and may be quite upsetting. A good working hypothesis, not scientifically proved, is that many viruses produce a great variety of clinical disease complexes, such as influenza, the common cold, sinusitis, canker sores, sore throat, postnasal drip, tracheitis, acute and chronic bronchitis, asthmatic bronchitis, atypical pneumonia, myalgias, torticollis, lumbago, sciatica, pleurodynia, acute upsets of the stomach and bowel, hepatitis, cystitis, herpes zoster, encephalitis and dermatitis herpetiformis. They remain alive in patients for a long time, measured in months more often than in weeks. Fever is often absent, even in pneumonia; it may be excessive when the situation is unimportant (as in an obstructive cold or acute diarrhea) — hence the temperature of the patient is not helpful in detection or in estimation of activity. Leukopenia is characteristic of the uncomplicated cases; leukocytosis usually suggests other invading organisms. The leukopenia persists for the duration of the disease, and may be accompanied by a moderate reduction in hemoglobin and red-cell count. The most reliable diagnostic sign is a cluster of minute vesicles on the soft palate and oropharynx. They are often discounted as herpes simplex or as being present in almost everyone most of the time, but so are respiratory infections. While they are visible, the patient may have one or other of the symptom complexes listed above in greater or lesser degrees, or he may deny them all, but all this time he is subject to spells of weariness and depression of spirit. Herein lies the peculiar importance of virus infections in old people: unless they are aware of what is going on in them, they must conclude that unexplained fatigue is age deterioration and depression is failing mental competence. Unnecessary inactivity, a gloomy view of the future and inadequate care in the prolonged mild cases can lead to serious declines. More active infections can upset any chronic disease that is present: coughing can produce heart failure and organic brain damage; cystitis can arouse pyelonephritis; diabetes is decompensated by the infection and the disordered food intake; and malnutrition follows closely on diarrhea and limited diets. Therapy is satisfactory for particular complications and acute situations. For the greater part of the course of influenza, which is without them, good treatment consists in avoiding cold cures and all possible drugs, and in encouraging rest when fatigue is present, normal activity when fatigue lifts, and a normal diet at normal hours. It is not an understatement to assert that the common cold or influenza is the most under-rated, undetected, overdosed and neglected health problem of old people today.

What is known about drugs for older people was reviewed with good sense and good humor by the late Dr. William T. Salter.[10] The much that needs to be known should be based on careful comparison of the action of the same drugs on younger people. For example, is the dosage of digitalis altered by age? There is an impression that it should be somewhat less, but that, properly used, the drug is of great value in the management of mild degrees of heart failure over a long period and of some value in lessening the alarm caused by tachycardia and extrasystoles. Can digitalis be used to lessen the rate of progress of cardiac hypertrophy or to lessen the incidence of active heart trouble in old people, the majority of whom have heart disease? Can any of the atropine series of drugs ever be used before all possibility of glaucoma has been ruled out?

It is agreed that hormones are not made in as large amounts in old age as in younger ages. One must determine whether such decrements cause trouble, and to explore the legitimate value of hormone supplements as well as to be conscious of

the harm that they can produce. What good can be accomplished by the male-sex hormone in old men that cannot be accomplished by facing facts and improving physical fitness, even when cancer of the prostate is alleged to be absent? What are the indications for female-sex hormones in women apart from alleviation of menopausal distresses? The unregulated use of them in a few women has seemed to enhance their hypertension. Although the basal metabolic rate falls in aging people, myxedema is rare; what symptoms can be attributed to the hypometabolism, and which of them can be safely controlled by thyroid, granting that coronary-artery disease and angina are not present? It appears to be wise to bring an elderly diabetic patient under insulin management slowly and to use as small doses as possible, because abrupt changes in blood sugar are not infrequently attended by coronary-artery or cerebrovascular accidents and because mental performance is more erratic in such patients vigorously treated. Particular caution must be exercised in administering ACTH and cortisone to old people because disasters due to salt and water retention and to the creating of hypertension are common. It is unfortunate that they have been extended to the general medical public while their therapeutic status in research clinics is not settled.

Sedatives and stimulants are used excessively today. Old people do best to avoid them as much as possible. The barbiturate group of sedatives produces serious addiction and dull behavior when taken daily. The widespread use of small daily doses of phenobarbital to control nervous tension and reduce high blood pressure is astonishing, for the evidence that it does neither is available to every practitioner who questions and examines his patients. Bromide poisoning is less common than formerly because the drug is not so popular. Chloral hydrate seems safe and is good for sleep in blocks of two to four hours. Stimulants are generally of the benzedrine family, now that strychnine is out of date. I have had no occasion to use them, but elderly patients have reported that the wakefulness that they produce is not of a sort that aids attentiveness; it is a tense feeling of having had too much coffee — if so, the reasonable use of coffee or tea might be better.

How to avoid the pitfalls of polypharmacy without becoming an unpleasant iconoclast is a problem in the art of medicine. Old people have many symptoms that, in retirement, can receive the attention they seem to deserve; they need interpretation, and the patients need guidance. But there often seems to be an inverse relation between the number of medicaments that the patients get or select for themselves and the time that their medical advisers give them. The harassed practitioner is tempted to save time by tossing a pill at a symptom, only to find the symptom triumphant or a changeling on the next visit. It takes much time to discover what the symptoms signify and to teach the patient to overcome one by a normal diet, another by neglecting the bowels, a third by work and physical play, a fourth by an afternoon nap and others by ignoring them. This seems to give the best results in terms of confident facing of the day, the night and the future; it is not long before the patient knows what to expect of medicines, what to report to his adviser and what to demand of himself. Practitioners who have been able to organize their personal lives and professional schedules so as to do all this believe that in the long run it does not take more time and that anyhow it is worth it.

Surgery can do a great deal more for the health problems of the aging than it is now called upon to do. Technical procedures have improved; the preparation of the patient for operation by placing him in good fluid, electrolyte and nutritional balance has made the operation itself and the postoperative recovery smoother,and anesthetics and antibiotics have solved many critical situations. Early ambulation has saved protein, bone and the will to get well. Old people seem to accept the hazards and pain of operations with greater equanimity than young ones. Good surgical teams are convinced that the age of the patient has little bearing on the outcome of their efforts. Hence a new tool is available to minify the threat of many diseases to continued living, and, what is even more important, to satisfactory performance.

Preventive surgery has a great role. Hernias should be repaired when they are discovered; so should relaxed pelvic floors (cystocele, rectocele, prolapse), and the gall bladder should be removed when gallstones are known to be present. It is true that one cannot foretell when a hernia will obstruct, if ever, and it rarely produces nervous indigestion. But it tends to get larger, it is an impediment to active physical work, and it can be used as an excuse for doing less and less; when it does become incarcerated the surgical experience is bad. The relaxed pelvic floor is a matter of daily annoyance. Gallstone disease is not to be estimated merely by the frequency and severity of colic; it is a real threat to life and to comfort, as noted below. Cancer should be operated upon in the hope both of cure and of making the remainder of life easier, for in old people its progress may be quite slow; to give all reasonable aid is to defend the patient.

Research in surgery is greatly needed. Advances in peripheral vascular disease, including localization of obstructive arterial lesions and ways of eliminating them, the role of sympathectomy and new ideas in handling varicose veins, promise much for old people. Orthopedic care of fractures has made great progress. Specific rehabilitation technics need to be applied more generously to aging patients who have suffered fractures or paralyses. The most

disabling situation for vigorous old people, the stiff hip (malum coxae senilis), requires much active study and experimentation.

Chronic diseases being those which persist for a long time, it can be assumed that few people reach the age of 60 without acquiring one of them and that most aging people have a variety of them. They cover nearly the whole field of internal medicine. A short summary of their incidence in one hospital is shown in Table 6. In recent years there has been a growing consciousness of their importance to the individual and society. Studies of them have been along two lines. There are the researches on particular diseases carried on by all teaching hospitals, medical schools and many clinics and

TABLE 6. *Incidence of Some Chronic Diseases in 7941 Patients over the Age of 61 on the Medical Service of the Peter Bent Brigham Hospital, 1913-1943.**

DISEASE	MEN	WOMEN
	%	%
Mental disorders	55.5	62.9
Hypertension — systolic pressure over 140	55.3	68.1
Hypertension — diastolic pressure over 90	30.8	37.2
Heart disease, clinical	55.4	55.5
Heart disease, pathological	71.5	71.7
Coronary-artery occlusion	25.0†	25.0†
Valvular heart disease	3.5	4.8
Peptic ulcer	9.2	4.4
Gallstones, clinical	7.1	18.5
Gallstones, pathological	18.1	38.0
Hernia	15.1	1.8
Nephritis, vascular and glomerular	5.5	3.8
Pyelonephritis	2.8	2.7
Hypertrophy of prostate	47.3	—
Relaxed pelvic floor	—	4.4
Pernicious anemia	3.1	4.3
Diabetes mellitus	6.8	17.2
Syphilis	7.6	2.3
Malnutrition	56.4	55.3
Arthritis, atrophic	1.6	2.7
Arthritis, hypertrophic (probable)	100.0	100.0
Neoplasms	15.7	12.1

*Adapted from Monroe.[9]
†Estimated.

clinicians. There are also attempts to survey all of one disease concerning its incidence and attempts to make a general focus upon all persistent disease by public-health workers and others. Both have their advantages and disadvantages. The overall attitude is summarized in the section on Chronic Illness in the Report of the President's Commission on the Health Needs of the Nation.[11] The individual attitude is expressed in that commission's section on the problems of the aging,[12] and a very sensible article from the insurance standpoint has been contributed by Mr. J. H. Miller.[13] Since physicians are still in the stage of learning how to deal with this whole group of diseases, several comments are necessary.

In the first place surveys of the incidence of chronic disease in a community and in the nation have been helpful, as in the detection of diabetes and heart disease. Sometimes they are vitally important, as in tuberculosis projects. They have also helped in the plans for needed hospital expansion and nursing and convalescent homes. But this work has to be done carefully so that in its solicitation of public support and in its report of findings undue fears are not created — fear of having the disease under study and resentment against the magnitude of the tasks discovered. Old people do not co-operate happily in any type of mass survey yet devised. The co-operation of children can be compelled because they are under the authority of parents and teachers; this authority is lacking for old people, and they remain the intense individualists that children would like to be. Many of them object to what they consider governmental or charitable interference, and for every one in whom a disease is discovered there are several who take a long time to get assurance that they do not have it. Furthermore, it is difficult to conduct a survey without undermining the confidence of the public in its practitioners' ability to diagnose and to treat the disease. Since the research team has special facilities in x-ray or other laboratory apparatus, it is assumed to have information about the most recent methods of treatment; hence sanatoriums and mass x-ray programs have taken tuberculosis out of the hands of the practitioner, perhaps properly, and diabetes-detection clinics lead to nutrition classes. But the practitioner remains on the job long after the survey is over.

Secondly, thorough studies of chronic diseases are done best in hospitals, particularly teaching hospitals with a variety of laboratory facilities and an adequate team of specialists who are incited to good performance by students. Such hospital teams are most likely to discover any differences that may exist in the behavior of disease according to the age of the patient, and to observe the interaction of one chronic disease upon another, and the effect of an acute disease upon a chronic disease. Staff and interns become interested in their patients and in collecting long-range data on their diseases, and are tempted to do what they cannot do well — that is, to take full charge of the patients. For patients who are seen by a number of specialists and a regularly changing set of interns and residents are often in doubt about whom to turn to when they are troubled people. They have many problems that are not exposed to strangers or to chiefs of staff. These are revealed only to their continuing friends, the chosen family medical advisers. Somehow a place must be found on the hospital research team for the general practitioner to make the studies valid and to take the best care of the patients.

Thirdly, it is coming to be realized that chronic disease resides in an individual, who goes on being an individual during, between and after his struggles with his disease. It is important to determine the effect of home and occupation, education, culture, play and hobbies on the incidence, severity and behavior of disease. In old people, the loss of these reasons for living has effects on disease. Medical investigators need to call on the skills

of sociologists, teachers, lawyers, employers and labor-union leaders to help them here, and such help might come if all these specialists could learn to speak a language intelligible to them all. And the general practitioner has his indispensable part again, because all old people are involved, they live everywhere and under all conditions, and they exercise their democratic right to choose how they handle themselves and their troubles. Since the problems are too vast for hospitals and public and private agencies, and since complex human beings require and request personal attention, the effective way to study the problems and handle the situation is to strengthen the general practitioner in numbers, in competence and in standing in the community. This is the joint responsibility of medical schools and medical societies.

The detection of chronic diseases in aging people will be helped greatly when adequate data have been accumulated not only on their incidence but also on their manifestations and course, in specific decades for large groups of all kinds. The assertions in Table 6 are based on the experience of one medical teaching service; they need to be supplemented richly from other hospitals. Care should be taken to describe the source of the clinical material, for to base conclusions entirely on studies of old people in old-age homes and almshouses would be about as intelligent as basing pediatrics on findings in children in orphan asylums. The thoroughness of the physical examination can be enhanced by awareness of the frequency of some findings, such as cataract or hypertrophied prostate; it must be precise in the description of nerve reflexes, since the mental status can be assayed only with sclerotic brain changes in mind, but it is often embarrassingly either rich or poor in helpful signs. Some clinicians comment on the normal findings in the chests of some old patients with pneumonic consolidation. Many are impressed with a coarse systolic murmur at the base of the heart; it may have no significance, but a change in its intensity may mean a change in the integrity of the heart, if it does not mean the extraneous influence of fever or excitement. Obviously, one needs detailed descriptions of physical findings, on people of successive age groups and also on people as they progress from one age to the next, before one can state with confidence what findings are to be expected at a given age, what are significant of active disease or malnutrition and what are suggestive of mental or physical strain.

History taking in old people is an art — and an ordeal. If it is to be reliable it must be accumulated in several sessions. Questions that are pressed hurriedly may not receive good attention or accurate recall. Poor memory is more often due to absorption with matters of immediate concern to the patient or to poor rapport with the physician. To arrive at the description of the presenting complaint only after devious excursions into the medical experiences of the relatives and neighbors and former medical advisers drives many a budding geriatrician back to pediatrics. But the logorrhea is not necessarily evidence of mental deterioration; it may represent a defense covering a confused and troubled person who is seeking to find out if his questioner can understand him. If there is not understanding, interpretation and general evaluation can be erroneous, and the interesting variations of symptoms due to other factors than years are missed. For example, it is often claimed that old people suffer less pain than younger ones. Some do. Others give textbook descriptions of pain.[14] Is there evidence that pain pathways are blocked by age or that cortical atrophy dulls appreciation? If demented people have pain they do not report it. But gallstone colic can become infrequent and less agonizing because the gall bladder and bile ducts thicken so that stones cannot move. Pain that is familiar can be tolerated better than a new distress; the hundredth renal colic may not be as important as an acute indigestion. The unceasing, painful impediment due to hypertrophic arthritis of the hip may be manifested only as cantankerousness. Life disciplines people. Old people have often had to stand pain and many other things. They march up to the dentist's chair unfalteringly, but grief can be a complete and prolonged anesthetic.

Considerations such as these are important in estimating the health problems of aging people. My experience is that many practitioners of medicine have a wealth of pertinent information, much of which is sound but very little of which is on record in textbooks. There is no area where information is less factual or more tinged with emotional bias than geriatric neuropsychiatry. My statistics[9] suggested that the majority of old people have mental disorders, but what is a normal standard? How rigid should the assessment be, and how far would the result differ in young and in middle-aged people? Probably few people pass their fifty-fifth year without feeling that they are losing mental competence or that others are beginning to think so; the retirement crisis intensifies this fear ten years later. When is a diagnosis of cerebral arteriosclerosis justified? Certainly not on the visualization of calcified arteries in x-ray films of the skull and nothing else. What can the diagnosis of generalized arteriosclerosis mean but antagonism, since no proof of the prevalence of hard arteries is offered? Rothschild's[15] evidence that symptoms do not depend entirely upon the type or degree of cortical damage has been taken to mean that there is no correlation between behavior in life and pathological changes at autopsy. Such reasoning is on a level with that of the psychologist who concluded that there is no such thing as mental fatigue because

he could find no way to measure it. It will take much precise observation of old people in life and minute study of their brains after death to construct sound data, but it needs to be done, and it has been started.

According to the records of the Peter Bent Brigham Hospital only 15 per cent of the patients over 61 years of age had clinical evidence of cerebral arteriosclerosis on the basis of abnormal reflexes and paralyses and on the assumption of sclerosis as the etiologic agent. Only a little over half of the 15 per cent showed personality changes that were probably related to the brain disease. No clues were discovered to why some patients with a stroke suffered degradation of personality and others did not, or to when or how fast the disease would progress. In some cases progression seemed due to lack of care; in others, custodial care in a nursing home or institution seemed to have speeded deterioration. There is no more horrible disease than cerebral arteriosclerosis with psychosis, in which the physical shell lingers interminably while less and less of its occupant is alive. The growth in numbers of such patients committed to institutions in recent years has been a cause for grave concern to mental-health administrators. All agree that, whereas cure is impossible, much can be done by vigorous and continuous care of the patient as a whole. When funds and personnel have been made available for this purpose, the results have been gratifying. But the important phase of the disease is early, while the manifestations are mistaken for senile eccentricity, while faults in judgment are creating havoc at home and at business, while legal restrictions are not applicable, and while the medical adviser summons his courage to extend his duty from patient to family and to employer.

Senility is a diagnosis that should be made reluctantly. It cannot be established at autopsy. In well developed form it is a fairly obvious clinical entity consisting of withdrawal from participation in living, absence of abnormal nerve reflexes and absence of active disease elsewhere in the body, particularly absence of hypertension and heart disease. The patients are usually to be found in congregate living situations such as old-age homes and public almshouses where there is no incentive to act and no decisions to be made. Senility affects perhaps no more than 2 per cent of all people over 61 years of age, the majority being very old.

Apart from typical psychoneuroses, ordinary psychoses and toxic-affective states due to acute anemia, high fever, uremia or heart failure, most disorders of mental health in old people stem from struggles with their environment. For want of a better term I have called them reactive depressions — that is, states of inferior mental and physical performance arising from inhibitions due to disease or to losses. Old people do not fear death as much as they dread the steps leading to it. When they lose friends, they resent in their mourning that the living cannot know how extraordinary their friends were; they do not know how to set about making new ones, and young people pass them by uncomprehendingly, just as they did in their own youth. When a woman loses her husband, she loses status in the society of couples; if she needs income, too often she has not been trained to manage the funds that she has; if she seeks a job she may have no skill to offer except housekeeping as a maid or as an extra in the homes of relatives. When a man loses his wife he loses also his housekeeper and his home. When a job goes, income and status and usefulness go with it. When house and neighborhood are cast off, the old person drifts. When an infirmity comes to one who has not kept up his habits of study and reflection and physical play, decisions and counterattack are ineffective. Rigid expressions are assumed to cover the secret dismay. Contemporary society is thought to be youth-centered, even by the old in good circumstances. Treatment of such depressions taxes the ingenuity and patience of the clinician wise enough to see them, but much can be accomplished. Large hospitals can learn from small ones the art of making patients keep occupied as normally as possible while they are sick. Reasons for living with interest can be found. Only one must not be content with halfway measures, for then the next reaction leads to nursing-home and custodial care, and solutions must be arrived at with full respect for the patient and with his willing co-operation.

Hypertension, it is now generally recognized, occurs in the great majority of aging men and women. It is known to be compatible with long life. Even very high levels of blood pressure can be sustained with good health for years. Practically never does hypertension cause headache in old people. Occlusions of coronary and cerebral arteries take place about as often with normal as with high blood pressure, for the real lesion is in the blood vessels. Renal failure is rare. One is almost convinced that the disease that the sphygmomanometer measures is a different one here. Then what does it tell? A rise above the patient's customary level can signify a somatic storm, such as a struggle with a stroke, or a hemorrhage from a peptic ulcer, or lobar pneumonia or an acutely obstructed bladder; in convalescence, the former level of pressure is regained. More often the rise in pressure reveals emotional tensions, as in women during menopausal symptoms, in men facing the retirement crisis and in all who are forced to cope with disagreeable situations. The clinician, therefore, uses the blood pressure as a clue to what is going on in the patient. Treatment is directed toward whatever that may be. Sedatives are clearly useless as hypotensive agents; in old people they may have just the opposite effect, because chemical dullness imposed on those who are clinging to what they fear is already dulled by

age increases the fear and the struggle. Exercise, particularly physical play, relaxes people and blood pressure, and invites a more confident facing of the problems that tended to raise the pressure. And the most rapidly acting therapy is freedom from solicitude about it on the part of the examiner.

(To be concluded)

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MEDICAL INTELLIGENCE

DR. ROCHESTER AND THE VERMIFORM APPENDIX: 1855-1867

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At the November, 1855, meeting of the Buffalo Medical Association, the main paper was a spirited defense of phlebotomy in pneumonia, which had been attacked as harmful by Austin Flint on a previous evening. A more modern note was struck by Dr. Thomas F. Rochester, Dr. Flint's assistant, who presented some pathological specimens. Dr. Rochester said that members would remember that he had exhibited at a previous meeting, two specimens of perforation of the intestine at the appendix vermiformis. In one of these cases, perforation had occurred from impacted fecal matter; in the second, it was consecutive to peritonitis, the perforation taking place from without inward. He then reported a third case, as follows:

CASE. James Rose, a coachman, of robust aspect, was taken sick on the 19th of October, and took oil to relieve what he supposed to be an attack of gravel, taking in all ℥ iv. On the 20th he was well enough to drive the carriage downtown. In the afternoon he had a sharp chill, with pain and dysuria, and again took oil and went to bed, stating that he had gravel which a cathartic would relieve. On the 21st, Dr. Rochester was called to see him. Found him suffering with spasmodic pain, the urine scanty and stained with blood. On introducing catheter found the bladder empty. There was also nausea and vomiting, with great tenderness of the abdomen, and well-marked signs of peritonitis. In reviewing the symptoms the most probable diagnosis seemed to be that he had been suffering from renal calculus, that the calculus had perforated the ureter, and the peritonitis was the result of urinary infiltration. Morph. gr. j. was given, to be repeated in an hour, and fomentations ordered. In the afternoon found him easier, and tossing about the bed, or lying on his side without the usual suffering attendant on change of position in this disease. On the 22d found his pulse diminished to 100. The morphine was continued with the addition of calomel. On the afternoon of the 23d he became collapsed and pulseless, and died that night. *Post-mortem:* The kidneys, ureters and bladder were healthy. The peritoneum exhibited a grade of peritonitis more severe and extensive than either of the gentlemen had ever met before. Large patches of gangrenous peritoneum were scattered over the visceral surfaces, some of them several inches square, but the center of inflammatory action was evidently about the caput coli. The smell being extremely offensive, the abdominal contents were removed to the dissecting-room of the college for examination. The appendix vermiformis was found firmly glued down to the caput coli, so much so that it required the knife to release its distal extremity. On turning it up, the perforation was found at the inferior surface of the junction of the appendix to the colon. *Within* the appendix was found a bean, which was the evident cause of death.

A little less than two years later Dr. Rochester, who had succeeded Flint as professor of medicine at the University of Buffalo, reported another case, which occurred in a child of unstated age. This boy, who had previously had an attack of peritonitis, was seen on the third day of his illness with severe abdominal pain and generalized abdominal tenderness. Dr. Rochester made a diagnosis of peritonitis, and the patient died three days later. At post-mortem examination generalized peritonitis with fecal matter in the lower portion of the abdominal cavity was found. The appendix, which was adherent to the rectum, was gangrenous and contained a bean-sized fecalith. In discussion Dr. Rochester said he considered this a much more common cause of peritonitis than was generally realized. He apparently found the literature on the subject meager although he noted that Rokitansky had indicated that perforation of the appendix was not infrequent.

Rochester had now reported to the Buffalo Medical Association 5 of these cases. No account of 3 of them is to be found — probably because of the secretary's erratic reporting of these meetings. Apparently, Rochester made no further effort to

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publish this work nor did he report any further cases until 1867. At this time he reported a case very much like that of the coachman. Originally, a diagnosis of right ureteral colic was made, but when Dr. Rochester saw the patient on the second day of his disease, he decided that the patient had "a localized peritonitis with disease of the vermiform appendix." When the patient died four days later, autopsy disclosed a gangrenous appendix "perforated by a large orifice" half an inch from its cecal attachment. Dr. Rochester's discussion indicated that his knowledge of disease of the appendix was considerable; he said that the condition could resemble renal colic, that it was a disease of young people and that it was "productive of a majority of cases of so-called idiopathic peritonitis particularly in the male sex." At this time he pointed out that the foreign bodies were rarely "cherry stones, beans, raisin seeds, etc., which they were commonly called but are usually concretions of hard fecal matter." He was sure that the condition was not always fatal. "An abscess could form and burst into the intestine or on the abdominal wall and he had seen one instance of each of these terminations." He commented that Dr. Willard Parker had intervened surgically for this condition successfully (he had drained an abscess) and pointed out "that in the case he reported tonight, operation might have succeeded; the disease was confined to the appendix exclusively; it could have been removed entirely but this could not be foreseen or conjectured even and the event might have been just as fatal." In his opinion "the possibilities of a spontaneous favorable issue are greater than the probability of successful surgical operation." He stated that he had now seen 11 cases of disease of the vermiform appendix.

The advanced ideas presented by Dr. Rochester on these three occasions were received without noticeable disagreement from the Association. In fact discussers appeared to accept the ideas, although it would be difficult to decide how much of this represented deference to professorial power. Rochester himself never presented any paper on the diseased appendix, and obituaries at his death in 1887 made no mention of any contributions on this subject. The rapid and apparently independent progress made by Dr. Rochester in his understanding of what is now known as appendicitis was noteworthy. He discarded the without-inward hypothesis early, for it is only mentioned in his first 2 cases. His recognition that the organ was subject to "catarrhal inflammation" and his theorizing about the possibility of extirpation gave evidence of a real understanding of the disease. His thought that extirpation was at least as dangerous as the disease may have been correct in preantiseptic 1867. As Burke has indicated in his scholarly article on the history of appendicitis, a number of physicians and surgeons appreciated the fact that the vermiform appendix was a source of disease. It does not appear that any of them realized its frequency or the possibility of its being consistently and successfully treated by surgery. The article by Fitz in 1886, however, radically and rapidly changed that; the rules given for the treatment of the disease are almost entirely acceptable to the modern surgeon.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39331

PRESENTATION OF CASE

First admission. A seventy-two-year-old retired statistician was admitted to the hospital on account of persistent bilateral calf tenderness.

For the past three years the patient had visited his physician because of poor circulation in both lower extremities. About six weeks before admission he began to experience pain in the legs after walking. The pain became more severe and was associated with calf tenderness, and he was referred to the hospital with the diagnosis of phlebitis.

Physical examination showed a thin man in no distress. The general examination of the chest and abdomen was negative. The skin of the legs was atrophic, and there was minimal bilateral ankle edema. Femoral and popliteal pulsations were diminished; there was marked calf tenderness. The temperature, pulse and respirations were normal, as was the blood pressure.

A urinalysis was negative. The blood hemoglobin was 9.5 gm. per 100 cc.; the blood sugar and nonprotein nitrogen were normal. A stool specimen was guaiac negative.

On the day of admission an uneventful bilateral common-femoral-vein ligation was performed, a clot being found in the vein above the profunda branch on the left.

Additional questioning disclosed that during the past three months the patient had lost his appetite, had vague abdominal distress made worse by eating and had lost 10 pounds. In view of this information and the low blood hemoglobin, a gastrointestinal series was done. This showed a normal esophagus, stomach and duodenum. The patient was given two transfusions, which raised the hemoglobin to 10.3 gm. per 100 cc., and was discharged on the thirteenth hospital day to a rest home.

Final admission (about one month later). In the interval the patient had continued to have anorexia and weight loss. He had had a cough during the few weeks before admisson but no chills or fever. Intermittent lower abdominal pain had become more frequent, lasting from one to four hours and subsiding spontaneously. During the forty-eight hours before admission, the pain in the abdomen had become constant, steady and localized to the mid upper abdomen. He had eaten practically nothing during those two days and had regurgitated what he did swallow.

Physical examination showed an emaciated man with a dry skin. Breath sounds and tactile fremitus were diminished in the left lower lobe posteriorly; however, these cleared somewhat when the patient coughed. The abdomen was slightly distended, and there was a hard, tender plum-sized mass in the course of the upper descending colon. Below this point the colon was not palpable; the transverse colon was easily palpable to the region of the mass. Palpation of the mass intensified the almost steady pain of which he had complained on entry. The mass was soft and not prominent at the times when the pain was minimal. The prostate was of normal consistence and three or four times the normal size. Rectal examination was otherwise negative. Findings in the legs were as before except that now the left femoral pulse was absent.

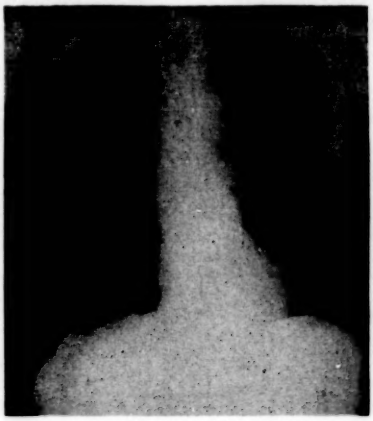

FIGURE 1. *Roentgenogram of the Chest.*
Multiple masses are present in the right and left lungs.

A urine specimen had a specific gravity of 1.012 and gave a + test for albumin; the sediment contained many red cells and occasional white cells per high-power field. The blood hemoglobin was

12.8 gm. per 100 cc., and the white-cell count 14,400, with 80 per cent neutrophils, 19 per cent lymphocytes and 1 per cent eosinophils. The serum nonprotein nitrogen was 18 mg. per 100 cc., and the sodium 128 milliequiv., the potassium 5.3 milliequiv., and the chloride 93 milliequiv. per liter.

A roentgenogram of the chest disclosed a sharply defined lobulated mass, measuring about 4 cm. in diameter, in the right middle lobe (Fig. 1). There was also an ill-defined mass, in the posterior basal segment of the left lower lobe close to the costophrenic angle. Old calcified scars were present in the left lower lobe laterally; in the left third interspace there was a rounded shadow, which could have been another scar. Lying at the right tracheobronchial angle was a lobulated soft-tissue mass

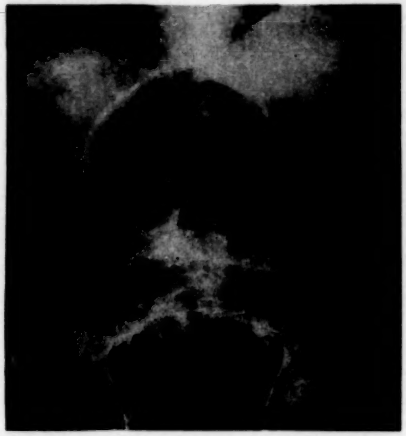

FIGURE 2. *Plain Roentgenogram of the Abdomen. Note the marked distention of the colon to the distal transverse portion.*

measuring about 4 cm. in diameter. The lung fields in general appeared emphysematous. There was wedging of one of the midthoracic vertebral bodies, possibly the eighth. The heart shadow was prominent in the region of the left ventricle, and the aorta was very tortuous. A plain film of the abdomen showed a large amount of gas in the colon, chiefly in the ascending and transverse portions, and there was considerable gas in dilated loops of small bowel (Fig. 2). There was an arcuate calcification in the lower abdomen to the right of the spine from the level of the third to the fifth lumbar vertebra. On two attempts at barium-enema examination, the barium passed only to the splenic flexure, but no definite lesion was outlined in this region (Fig. 3).

In the hospital the patient became disoriented; the abdomen was more distended, and loops of small bowel were palpable. Peristalsis was less active. On the third hospital day a cecostomy was performed, relieving the distention for several days. On the sixth hospital day the white-cell count

FIGURE 3. *Barium-Enema Examination. Arrows point to the left upper abdominal mass, partially outlined by air and barium.*

was 21,300, with 84 per cent neutrophils. One examiner thought that he could definitely palpate a mass the size of a tennis ball just above and to the left of the umbilicus. A temperature of 101°F. developed, and the patient took nourishment poorly. He gradually weakened; the left leg became gangrenous, and he died quietly on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MICHAEL E. DE BAKEY*: Briefly to review the essential findings, a seventy-two-year-old (obviously elderly) man, who was apparently undernourished and emaciated, complained on his first admission to the hospital of bilateral tenderness in the calves of his legs and intermittent claudication for several months. At that time the diagnosis of phlebitis appeared to be justified and was confirmed by operation, which demonstrated the presence of a thrombosis of the left femoral vein. One of the most significant findings, however, was the marked anemia — hemoglobin of 9.5 gm. per

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100 cc. The studies at that time, which were apparently directed toward the possibility of a gastrointestinal lesion causing the secondary anemia, showed no abnormal findings. I assume that x-ray studies of the chest at the time of the first admission did not reveal any of the subsequent findings in the chest.

DR. DANIEL S. ELLIS: Chest films were not taken on the first admission.

DR. DE BAKEY: Is not fluoroscopy of the chest usually done routinely at the time of a roentgenologic examination of the gastrointestinal tract?

DR. STANLEY M. WYMAN: Yes; it is. In retrospect the films from the gastrointestinal series do show lesions in the lower part of the chest.

DR. DE BAKEY: Therefore, I should assume that the roentgenographic chest findings demonstrated on the second admission were present at the time of the first admission a month previously and that further investigation of this matter should have been continued. In any case a month later, when he was readmitted, the patient was obviously much worse generally. A cough of two weeks' duration, not associated with chills or fever, had developed. He was complaining of more definite findings in the abdomen, with pain of an almost persistent character, at least subsiding only periodically. The pain was associated with marked anorexia and weight loss but apparently no vomiting. He certainly was not eating during the last few days or even drinking water because he was dehydrated on admission.

It is somewhat difficult to evaluate the plum-sized mass in the abdomen because at one time it appeared to be hard and quite tender and on another occasion soft and not prominent, and at still another time it was palpated as a mass the size of a tennis ball. I assume, therefore, that it was a definite mass; it was associated with pain, which suggests that it was producing some peritoneal irritation; the fact that fever and leukocytosis subsequently developed suggests that it was associated with possible infection. In light of the abdominal distention and the x-ray findings of a large amount of gas in the ascending colon and dilated loops of small bowel I believe that this mass involved the bowel, and that it may have resulted in localized perforation or peritonitis. The relation of this mass and these findings in the abdomen to the masses that were present in the chest I think constitutes part of the problem in the diagnosis of this case. Perhaps at this point it would be desirable to view the x-ray films.

DR. WYMAN: The films of the original examination of the upper gastrointestinal tract show no intrinsic disease in the stomach or duodenal cap or loop. There is considerable vascular calcification, and, as Dr. De Bakey has pointed out, a mass in the left lower-lung field is seen in retrospect in this film. I think a second mass was present in the right midlung field lying in the right middle lobe probably at the time of this original examination. Other findings in the chest (Fig. 1) include a small lesion in the left middle portion that is discrete and rounded and a calcified scar far laterally on the left side. There is evidence of old pleuritis in the left apex and perhaps in the right, and there is some sort of lesion in the right tracheobronchial angle that certainly suggests enlarged lymph nodes. The chest in general is much increased in size and consistent with severe emphysema.

DR. DE BAKEY: Is this the arcuate calcification?

DR. WYMAN: Yes; the arcuate calcification presumably represents the aorta.

DR. DE BAKEY: Do you have any lateral films that show that?

DR. WYMAN: No; we do not.

DR. DE BAKEY: Is this in the base?

DR. WYMAN: I think the lesion lies anteriorly in the region of the middle lobe, but I cannot be certain of that. The second large lesion lies more posteriorly in the left lower lobe. Without fluoroscopy it is difficult to be certain of the exact location of these things.

The principal problem is shown by these abdominal films. When the first films were taken there was evidence of a great dilatation of the colon up to the left transverse portion, and there was dilatation of several loops of small bowel (Fig. 2). There was only a small amount of gas in the descending colon. Two attempts were made to outline a mass by barium examination. Many diverticula were present in the descending colon. I cannot outline the mass with any great degree of certainty, but there is a rounded shadow outlined in part by air and here perhaps by barium (Fig. 3) on several of these films. This probably represents the mass that the examiners were feeling at various times.

DR. DE BAKEY: Is this finding an intrinsic mass?

DR. WYMAN: I think it is an intrinsic mass in the left transverse colon or in the region of the splenic flexure.

DR. DE BAKEY: Would you regard this as wedging in the spine?

DR. WYMAN: I think it represents a demineralized kyphotic spine.

DR. DE BAKEY: It seems to me that the manifestations of marked weight loss, anemia and weakness with these findings certainly suggest, on a clinical basis anyway, the presence of a malignant lesion. The patient apparently had manifestations first in the form of venous thrombosis; yet the findings suggested a malignant lesion. It is interesting to reflect upon the association of a malignant lesion of an internal organ and venous thrombosis. That is a well known and old observation, but I do not know that it is well established. There is some reason to believe, on the basis of statistical evidence, that venous thrombosis is more frequently associated with the presence of cancer even though it

may be hidden than with the absence of cancer; some have even attempted to relate it to cancer of certain organs — for example, the pancreas.

The findings, particularly the chest findings, which I think are prominent, I do not believe can be explained on the basis of pulmonary infarction from the thrombosis. For one thing, pulmonary infarction is less likely to produce a lobulated lesion, and it is certainly not likely to produce shadows in the mediastinum that are so suggestive of lymph-node involvement in that region. The patient's pulmonary manifestations were also not characteristic of pulmonary infarction, at least of that extent. I should not be inclined to explain the pulmonary shadows observed here on the basis of pulmonary infarction even though the patient had venous thrombosis; I believe that they are more suggestive of a malignant lesion of the lung, with associated involvement of the mediastinal lymph nodes, particularly of the right tracheobronchial lymph nodes, which are seen in this x-ray film.

It is interesting to speculate about the possibility of two separate lesions, one in the lung and one in the bowel, but statistically I think it is unlikely that two separate lesions would explain such findings. We know that carcinoma of the lung, which I strongly suspect was present from this x-ray film, can be associated with widespread cancer. The most frequent sites of distant metastases are the regional lymph nodes, the liver, the opposite lung, the bones and the brain. We have recently collected a consecutive series of cases of carcinomas of the lungs in which the brain was studied post mortem very thoroughly, and found 30 per cent with metastases to the brain, so I think it is much more frequent than we had previously believed. Carcinoma of the lung that metastasizes to the bowel is relatively unusual, but it does occur and that is a possible explanation of this lesion in the bowel. One might also reverse the explanation by saying that it arose originally in the bowel and metastasized to the lung. That might be a more logical explanation for the bilateral involvement of the lungs; if the lesions are malignant one would expect such bilateral involvement of the lungs by metastatic carcinoma from some other site. The fact that there was mediastinal involvement persuades me that it was not primary in the bowel. Mediastinal lymph-node metastases are more likely to occur with primary carcinoma of the lung than with metastatic carcinoma to the lung. It is relatively unusual for carcinoma metastasizing to the lung to be associated with mediastinal lymph-node metastases as well.

Finally, I have not satisfactorily explained the gangrene of the left leg and the arcuate shadow in the chest. The arcuate shadow may have been a fusiform dilatation or distortion and lengthening of the aorta. This much calcification suggests extensive arteriosclerosis and atherosclerosis, and I am inclined to believe that thrombosis of the femoral artery developed on that basis; with arteriosclerosis and the marked emaciation and deterioration in general condition such thrombosis is much more likely to occur.

DR. BENJAMIN CASTLEMAN: Do you believe that the patient had two separate tumors?

DR. DE BAKEY: I cannot say with any degree of conviction that he had two separate tumors, but I am more inclined to consider the lesion in the lung as the primary one; I am quite impressed with the mediastinal lymph-node involvement and I am also impressed with the statistical frequency of carcinoma of the lung. In our hospital it is one of the most common sites of carcinoma in the male. I should be inclined to think it is a better way to explain the findings.

The patient had evidence of infection, with fever and leukocytosis, and had tenderness and a painful mass in the abdomen so I wonder about the possibility of peritonitis from a lesion in the bowel, with perforation. I am inclined to consider either that these were two separate lesions or that the primary was in the lung rather than the other way around.

DR. CASTLEMAN: Do you want to know whether he was a smoker or not?

DR. DE BAKEY: I assume that he was.

DR. F. THOMAS GEPHART: He smoked cigarettes rather heavily up until three years before admission, when he had trouble with arteriosclerosis.

DR. WARREN POINT: Do you think all the shadows in the lung were due to carcinoma, Dr. De Bakey?

DR. DE BAKEY: No; one looks like an old healed lesion. Some may or may not be; I just cannot say because they are too ill defined.

DR. GEPHART: I knew this patient for some time. He had had many attacks of sinusitis in the past and had had numerous operations; for many years he had irrigated his own sinuses and had a large amount of postnasal drip. Therefore, we thought some of the lung lesions could have been a chronic pneumonitis. Moreover he had a back injury some years previously, with the compression fractures that explain that finding. In addition, about three weeks before the onset of the phlebitis, there was an episode of apparent cerebral thrombosis, with dizziness and thickening of speech, that we believed contributed to the loss of appetite that had begun at about that time. At no time before the final admission to the hospital had the patient had any bowel symptoms beyond the pain associated with eating; there was no constipation, diarrhea or tarry stools.

DR. DE BAKEY: The negative guaiac test on the first admission suggests that he did not have the lesion at that time.

DR. ROBERT R. LINTON: Aside from Dr. Gephart, I think I saw this patient more often than anyone else. When he came to me first for his peripheral arteriosclerosis, it was obvious from his age and the extensive arteriosclerosis of the lower extremities there was nothing to do but teach him how to take care of the condition. The final episode that began with venous thrombosis aroused my interest as it has Dr. De Bakey's, especially in view of the marked anemia. I was looking for a cancer in the gastrointestinal tract but only got as far as an upper gastrointestinal series when I was discouraged by the other physicians on the case from further studies and probably rightly so as evidenced by the final findings, since nothing could have been done for the numerous lesions. One feels remiss, however, in not having completed the examination once it had been started.

DR. DE BAKEY: I might say, in the light of the arcuate shadow there, that the possibility of a leaking aneurysm is to be considered although it would not explain the other findings that were present. Leaking aneurysm may ooze very slowly and produce intermittent episodes of severe pain, and the patient can go on for months. I know of a patient who went two years before he had another leaking episode. It is associated with some leukocytosis, some fever, certainly tenderness and a mass that may not be calcified as one would expect so that one can be fooled by that type of finding. The x-ray finding of the presence of the calcified shadow outlining such a mass is of considerable significance in these aneurysms, particularly in the abdominal aorta.

CLINICAL DIAGNOSIS

Carcinoma of splenic flexure, with metastasis to lungs.

DR. MICHAEL E. DE BAKEY'S DIAGNOSES

Primary carcinomas of lung and colon or carcinoma of lung with metastasis to colon.
Aortic aneurysm.

ANATOMICAL DIAGNOSES

Undifferentiated adenocarcinoma of lung, with metastases to regional lymph nodes, lung and small and large intestine.

Intussusception of metastatic polypoid carcinoma.
Arteriosclerotic abdominal aneurysm.
Thrombosis of both iliac arteries.
Lipoid pneumonitis, multiple foci.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy disclosed that the abdominal shadow was, as Dr. De Bakey suggested, a large arteriosclerotic aneurysm, which began below the level of the renal artery and extended down almost to the iliac artery. Both iliac arteries were practically occluded, with more occlusion on the left side, which accounted for the terminal gangrene. In the right upper lobe there was a carcinoma that was markedly necrotic and involved the wall of the bronchus of the right upper lobe. Microscopically, this was an undifferentiated car-

FIGURE 4. *Small-Bowel Metastasis Presenting as a Polyp.*

cinoma. In the regional lymph nodes upon which Dr. De Bakey correctly placed so much emphasis we found some evidence of true gland formation so that this was probably an undifferentiated adenocarcinoma. Most of the other masses seen in the lung were foci of lipoid pneumonia (we learned later that the patient had taken mineral oil for many years). Large, fat-filled spaces made up, for example, the mass in the right middle lobe, which measured 5 cm.; all the masses on the left were similarly involved. Two small nodules in the right lower lobe proved to be metastases from the primary tumor. We found in the small bowel eight nodules that were metastases from the tumor in the lung. These were all in the submucosa, and some of them were polypoid. The fact that there were so many of these small nodules, which did not have the microscopical appearance of adenomatous polyps, is good evidence that they were all metastases from the primary tumor in the lung. They were quite anaplastic and resembled the pulmonary lesion. Some were merely submucosal; others had elevated or eroded the mucosa, and some were drawn out by the propulsion of the small bowel to produce a small polyp with a true pedicle (Fig. 4). Ordinarily, when we see numerous polypoid metastatic lesions in the small bowel, we think of a malignant melanoma, but the histologic findings in this case did not suggest a malignant melanoma. I believe they are consistent with metastases from the primary tumor in the lung (Fig. 5). The mass that was felt just before death was an intussusception in the transverse colon led by a similar metastatic lesion in the ascending colon (Fig. 6). This mass was felt in the region of the splenic flexure although it had started in the bowel below the he-

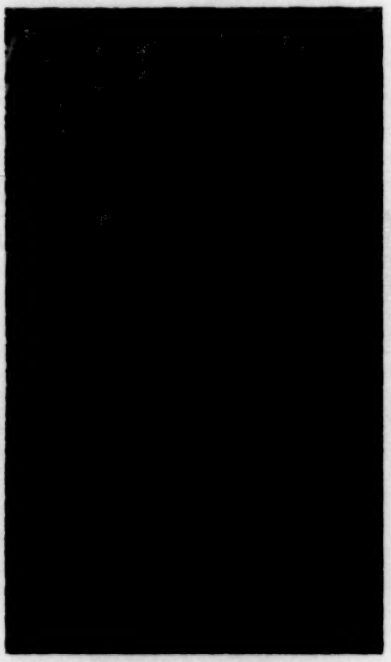

FIGURE 5. *Higher Magnification of the Lesion Shown in Figure 4. Note the normal mucosa at the top and submucosal anaplastic carcinoma.*

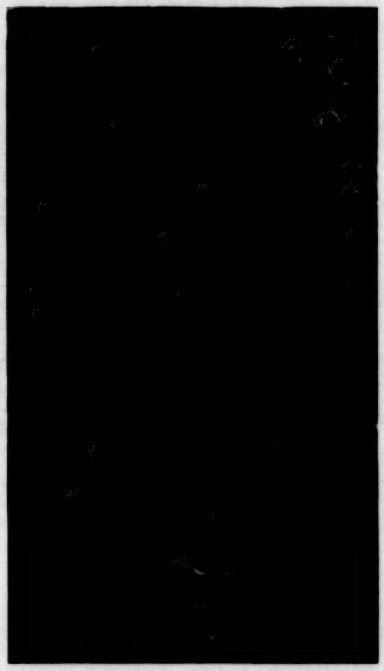

FIGURE 6. *Intussusception of the Polypoid Metastasis in the Transverse Colon.*

patic flexure. The tip was quite necrotic and was apparently the cause of the intermittent pain.

DR. DE BAKEY: This is an unusual form of metastasis and an unusual complication. Although there were some features against the diagnosis of intussusception — including particularly absence of blood and mucus in the stools, negative guaiac test and absence of the characteristic coil-spring roentgenographic pattern — there was one suggestive clue, which now assumes added significance. This was the fact that the hardness of the mass varied with the intensity of the pain. Since this is a characteristic feature of intussusception it is apparent that we should have assigned greater significance to this manifestation.

CASE 39332

PRESENTATION OF CASE

A forty-one-year-old man was admitted to the hospital complaining of a "spell."

He was in excellent health until ten days before entry, when, while sitting talking to a friend, he suddenly experienced a sensation that he was falling to the left from his chair. About a minute later he was conscious of a "numbness" that began in the left lower part of the thorax and spread to involve the left leg and left arm. Coincidentally with this he fell to the floor. He remembered hearing his friend call for an ambulance, but then recalled nothing until, on regaining consciousness about an hour later he was aware of a sore tongue, mild generalized headache and a diffuse weakness and numbness of the left side. He was admitted to another hospital, where the weakness of the left side was confirmed and a left Babinski sign demonstrated. A blood serologic test, cerebrospinal-fluid pressure and cell count, right percutaneous carotid angiogram and skull x-ray films were reported as normal. The left hemiparesis cleared completely within four days. The numbness of the left side was more persistent, especially in the left lower leg, and even after sensation became normal, he continued to have frequent, transient episodes of numbness limited to the left lower leg. These were unassociated with weakness or involuntary movements. At times these episodes were associated with soreness of the left anterolateral costal margin, occasionally with the feeling that he was falling out of bed to the left. During the two days before admission he frequently misjudged the position of the left arm of his wing chair when he attempted to support himself in arising.

The past history and review of systems were noncontributory. The patient specifically denied early seizures, head injury, visual and olfactory hallucinations and vertigo. His wife had noted no change in his behavior. There was no pertinent family history.

On examination the patient did not appear ill; he was well oriented and direct in answering questions. Several nontender, soft subcutaneous nodules were palpable in the skin of the abdomen. Examination of the heart, lungs and abdomen was negative. The skull, cranial nerves and motor systems were normal. There was questionable exaggeration of the left knee jerk, but otherwise the tendon reflexes were active and equal. There was no Babinski sign. Complete sensory examination was negative except for inability to recognize numbers written on the skin (absent graphesthesia) over the dorsum of the left foot.

The temperature was 98.6°F., the pulse 88, and the respirations 18. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a white-cell count of 14,200, with

FIGURE 1. *Pneumoencephalogram (Lateral View).*
Lower arrow points to depression and flattening of the posterior portion of the right lateral ventricle. Upper arrows point to the linear calcifications.

84 per cent neutrophils, 10 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils, normal appearing red cells and a hemoglobin of 15.1 gm. per 100 cc. A blood serologic test was negative. On lumbar puncture the cerebrospinal fluid was under a pressure equivalent to 155 mm. of water and contained 340 red cells per cubic millimeter and no white cells; the protein was 36 mg. per 100 cc. An x-ray film of the chest was normal except for a question of linear atelectasis at the right base. A pneumoencephalogram demonstrated a slight shift of the ventricular system to the left side and depression and flattening of the posterior portion of the right lateral ventricle (Fig. 1 and 2). A few irregular streaks of calcification were noted in the brain substance adjacent to the ventricular defect.

On the day after admission a seizure was observed. This began with a diffuse numbness of the left side of the torso and was followed in a few seconds by numbness spreading to the left arm and leg. This was associated with clonic contractions of the muscles of the left side of the torso and the left leg and, to a lesser extent, the left arm. The patient was awake and responsive throughout the seizure, which lasted about a minute. On the fifth hospital day, an operation was performed.

FIGURE 2. *Pneumoencephalogram (Anteroposterior View). Note the slight depression of the ventricular system toward the left. Arrows indicate the positions of the calcifications.*

DIFFERENTIAL DIAGNOSIS

DR. H. THOMAS BALLANTINE, JR.*: The problem in this case is to diagnose the cause of two seizures in a forty-one-year-old man who, before their appearance, was believed to be in good health. These seizures were of a particular type, characterized by a feeling of numbness over the left side of the body and followed, on one occasion at least, by clonic contractions of the left side of the torso, the left leg and to a certain extent the left arm. Such a pattern of convulsive movements is called a focal or jacksonian seizure, and I shall take as my guide in this discussion a quotation from the writings of Hughlings Jackson,[1] whose name is intimately associated with this symptom complex:

> In the class of seizures I speak of in this paper, the spasm begins comparatively deliberately in (1) the hand or (2) in the face or tongue, or in both these parts or (3) in the foot. This is the order of frequency of place of onset, the onset being usually always the same in the same patient. The evidence from morbid anatomy, agreeing with that of the physiological experiments alluded to, is that there is in these cases cortical disease, and that the part of the cortex affected is within the mid-region of the brain — of convolutions bordering the fissure of Rolando.
>
> In some cases, if not in most, there is premonitory numbness, tingling or some other abnormal sensation in the parts first seized by spasm; evidence, I think, that the centers engaged are not wholly motor.

This excerpt from a paper that was published seventy-two years ago applies exactly to the problem under consideration because in this patient I believe that there was cortical disease and that the centers engaged were not wholly motor. The onset of the convulsions on two occasions was with a feeling of numbness, and it is also apparent that after the seizures the sensory findings were slightly more prominent than the motor. Furthermore, most of the clonic contractions were in the torso and the left leg and to a lesser extent in the left arm. I deduce from this evidence that the greater part of the cortical disease lay posterior to the fissure of Rolando on the right, high and rather near the midline.

Having come to the conclusion that this patient had a lesion high in the right parietal area in or near the fissure of Rolando, I now must classify the pathologic process. In these exercises it is usual to start with the less likely diagnoses first and try to build to a climax. I find this rather artificial, for in all clinical evaluations of a patient, I, at least, tend to go directly to the diagnosis I think most likely and to try to defend it in my mind against other possible diagnostic entities. Furthermore, when a surgeon hears of a patient who, in middle life, has the first of a series of seizures and those seizures are of a focal or jacksonian type, an alarm bell rings in his consciousness and a great sign floats across the horizon that reads "space-taking lesion." Until the presence of a space-taking lesion is disproved by all the diagnostic facilities at his disposal the surgeon is likely to be morose, restless and more than usually irritable. To save myself that irritation, I shall assume that this man had a space-taking lesion in the right posterior parietal region. Statistically, tumor is more likely than any other condition. Having said that I must explain the fact that the symptoms came on suddenly and I shall assume that the reason for the sudden onset was that the tumor began to grow in a silent area of the brain and only caused symptoms when it began to encroach on the sensorimotor area of the cortex.

Sepsis in the form of a chronic granuloma or a beginning brain abscess must be considered particularly in view of the white-cell count of 14,200, with 84 per cent neutrophils. But the lack of a focus of infection elsewhere in the body and the fact that there were no white cells in the cerebro-

*Assistant neurosurgeon, Massachusetts General Hospital.

spinal fluid makes me doubt whether a septic intracranial process was present.

The 340 red cells per cubic millimeter in the cerebrospinal fluid raises the question of a cerebrovascular accident as the cause of the seizures. I am inclined to attribute the presence of these red cells to the lumbar puncture although nothing was said in the protocol about such a possibility. The patient was relatively young; he had no hypertension, and his neurologic deficit between seizures was not great. On these grounds, alone, however, I cannot exclude the presence of subcortical blood clot. Old thrombosis of the carotid artery or of other intracranial vascular channels, with subsequent scar formation, is, I think, unlikely; it is my impression that thrombosis ushered in by a focal fit as the first symptom is unusual. Subdural hematoma must be considered and can give rise to unilateral symptoms, but the seizures, in my experience, are usually not so focal in character and onset, and the patient is almost never as well between attacks as this patient was said to have been.

Cerebral scars are a common cause of focal or jacksonian seizures but there was no evidence of any previously existing intracranial condition that would lead to scarring; therefore, I must discard that diagnostic possibility.

I wonder if we could see the x-ray films?

Dr. Stanley M. Wyman: The skull films show a slight depression of the right lateral ventricle involving the posterior portion of the body (Fig. 1). This is best seen stereoscopically. There is a series of linear calcifications lying in this region corresponding to the area of depression of the lateral ventricle. This apparently is fairly deep in the brain substance and is seen in other projections at this point. There is minimal displacement of the entire ventricular system toward the left (Fig. 2).

Dr. Ballantine: Is the difference in height of one ventricular shadow over the other significant?

Dr. Wyman: I think it probably is. In this film, a fairly true lateral view, there is a definite downward displacement of the right lateral ventricle posteriorly.

Dr. Ballantine: The shift is minimal, but the flattening is readily apparent, as are the streaks of calcium. The stereoscopic view in addition to the very slight shift confirms the impression that this was a right-sided lesion and the flattening of the posterior portion of the right lateral ventricle places the process high in the posterior parietal region, so I think I can say fairly confidently that there was a space-taking lesion in the area described.

It now remains to classify further the type of lesion that may have been present. For that I shall turn for help to the streaks of calcium overlying or adjacent to the ventricular defect. The presence of that calcification eliminates almost at once the possibility that a cerebrovascular accident was responsible for the symptoms. Although it would be possible to assume an arteriovenous abnormality, which had bled into the white matter of the brain, these streaks of calcification do not look to me like those usually seen in such arteriovenous abnormalities, and the course — the sudden seizure and the almost complete recovery thereafter — does not suggest such a diagnosis. A chronic granulomatous mass, such as a tuberculoma, gumma or cysticercoid lesion, is another diagnostic possibility but highly improbable in the face of the lack of other evidence of such conditions. I believe that this calcification was within the substance of a tumor. Dandy[2] has reported that about 15 per cent of brain tumors in his series demonstrated some degree of calcification. Meningiomas and the slowly growing gliomas show calcification almost equally in the supratentorial region. The calcium in a meningioma is due to psammoma bodies and generally presents a stippled appearance; it also may be within the capsule of the tumor.

I tend to believe that this calcification was in a tumor of the glioma group. Although both astrocytoma and oligodendroglioma can show calcification, it has been my experience that oligodendroglioma shows calcification more often than astrocytoma does. Oligodendroglioma is a rare tumor; we see a great many astrocytomas. Although I am on unsafe ground in this exercise in trying to pin a diagnosis down so exactly, I shall choose oligodendroglioma as the histologic type of tumor.

In summary, this forty-one-year-old patient, in previous good health, had the onset of two jacksonian seizures and therefore was finally subjected to craniotomy. Evidence derived from the neurologic examination and pneumoencephalogram pointed to a space-taking mass in the right posterior parietal region. I believe this mass was a tumor and that in all likelihood it was an oligodendroglioma.

A Physician: Could it have been a neurofibroma?

Dr. Ballantine: That would be a most unusual location for a neurofibroma, which we usually see on nerve trunks. I should have mentioned that calcification is seen in the so-called suprasellar cysts, the Rathke-pouch cysts, but certainly this was not in the suprasellar region, and calcification is also seen in dermoid cysts, which may occur anywhere in the intracranial cavity but, in my opinion, are usually more or less contiguous with some portion of the skull. I do not think this was a dermoid.

Dr. Farahe Maloof: Do you see calcification in metastatic lesions to the brain?

Dr. Ballantine: No; I have never seen it. The presence of calcification usually indicates a chronic, slowly growing lesion.

Dr. Edward P. Richardson, Jr.: I do not think any of our material has shown calcification in a metastatic carcinoma of the brain.

DR. WILLIAM H. SWEET: I have seen massive calcification in an osteogenic sarcoma, metastatic to the brain from a primary lesion in the thigh and a secondary lesion in the lung.

CLINICAL DIAGNOSIS

?Vascular lesion, parietal lobe.
?Tumor, parietal lobe.

DR. H. THOMAS BALLANTINE'S DIAGNOSIS

Oligodendroglioma, right parietal region.

ANATOMICAL DIAGNOSIS

Brain tumor: oligodendroglioma, right parietal region.

PATHOLOGICAL DISCUSSION

DR. RICHARDSON: Dr. Sweet, would you tell us about the operative findings?

DR. SWEET: This was Dr. Hannibal Hamlin's patient; Dr. Hamlin did an arteriogram, which showed good filling of the left carotid tree and no indication that either of us could make out of any abnormality in the filling. In the exploration that Dr. Hamlin and I did, we found that the precentral gyrus was readily identified by electric stimulation. There was firm tissue lying in the superior parietal region behind the postcentral sulcus that was obviously neoplastic. We extirpated the occipital and most of the parietal lobe right up to the postcentral gyrus.

DR. BALLANTINE: Was the calcium identified at the time of the resection, or did you do an *en bloc* resection?

DR. SWEET: We saw calcium in the specimen after it was removed.

DR. RICHARDSON: Microscopical examination of the tissue removed at operation showed a tumor composed of small cells with spherical nuclei and a clear round halo of cytoplasm surrounding the nucleus. The cells, of generally uniform size and shape, were densely grouped together, and were infiltrating the brain tissue at the periphery of the tumor mass. The stroma was made up of glial fibers, in which there were many irregular foci of calcification. There were no mitoses and no giant cells or other indications of rapid or disorderly growth. These histologic characteristics are typical of oligodendroglioma, an uncommon tumor of glial origin. Kernohan and Sayre[3] state that it formed about 10 per cent of all gliomas in their series, but in our material, it occurs with less frequency. Oligodendrogliomas are relatively benign, slowly growing tumors that generally occur in the cerebral hemispheres in late adult life. They frequently contain calcification, which, as in this case, may be visualized in x-ray films of the skull.

DR. HANNIBAL HAMLIN: I have examined the patient several times since he was discharged from the hospital. He has made steady progress and four months after discharge showed only minor residua of the left-sided motor deficit, which affected his leg more than his arm. He walked without difficulty and used his left hand well. His most serious deficit was a permanent left hemianopia. We believe that he is one person with a brain tumor who has been cured.

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FEWER APPLICANTS TO MEDICAL SCHOOLS

THERE is a widely current misapprehension that in the face of a dire need throughout the country for more doctors the medical schools annually turn away several times as many applicants as they accept. Actually in 1952-1953 nearly half of all applicants for admission to medical school were accepted (7778 acceptances out of 16,763 applications).

It is true that almost any one of the better known medical schools may receive requests for application blanks from five to ten times as many candidates as they can possibly admit. But this simply reflects the fact that applicants are simultaneously applying at several medical schools. If the number of applications made by residents of any given community is considered, it will be found that in most communities nearly half of all applications are successful. Generally, medical schools tend to favor the applications of those living in their own community — some to a much greater degree than others.

Another interesting fact that is not as widely known as it should be is that the number of students who wish to study medicine has declined sharply during the past four years. Fewer than 70 per cent as many applications were received during 1952-1953 as were made in 1949-1950. Of the schools in this area applications to Harvard were off 34 per cent, and those to Tufts 33 per cent and to Boston University somewhat less.

Many medical schools, in response to public demand, have been stretching their facilities to accept a few more applicants each year. If in 1953 a school accepts 120 out of 260 candidates whereas in 1950 only 110 of 300 candidates were accepted, it is obvious that because of decreasing numbers of qualified applicants there is now greater competition among the schools to attract the high-ranking student. Most medical schools are forced to accept men whom they would not have accepted four years ago. There is, in fact, a relative dearth of first-class material. Medical schools are no longer turning away good men. They are clamoring for more and better applicants.

Fortunately, the need for more doctors is not nearly as great as the public has been led to believe. In Massachusetts, for example, there are, numerically, many more physicians than are needed. Any lack of medical care in individual communities may be ascribed to other factors than the mere number of theoretically available physicians. One of these factors is the proper distribution of general practitioners.

ISONIAZID

THE highly encouraging therapeutic results reported from the use of isoniazid (isonicotinic acid hydrazide) in patients with tuberculosis has stimulated considerable interest in this agent. A number of studies recently published contribute greatly to an understanding of the mode of action of this antituberculous drug.

It is generally considered that the intracellular location and propagation of the infecting tubercle bacilli is one of several important factors that determine the response of the disease to chemotherapeutic agents. Living tubercle bacilli segregated inside macrophages and epithelioid cells that may not be penetrated by substances in the tissue fluids may persist during therapy, accounting for the failure of otherwise potent antibacterial agents to cure experimental tuberculosis in animals.

Recently, Mackaness,[1] at the Sir William Dunn School of Pathology at Oxford, described a method of determining in vitro the sensitivity of intracellular bacilli to various drugs. He used living isolated rabbit macrophages as a medium for the propagation of human and bovine tubercle bacilli growing as intracellular parasites and tested the activity of the drugs in this medium. Most of the drugs showed a marked reduction in activity against intracellular bacilli as compared to their activity in a culture medium in which the organisms are dispersed (Dubos-Davis medium). Thus, 25 microgm. of streptomycin per cubic centimeter was required to prevent the intracellular growth of the human virulent strain H37Rv, whereas in the liquid medium this culture was inhibited by 0.6 microgm. Isoniazid, on the other hand, was found to be equally active against the intracellular bacilli and against those grown in the Dubos-Davis medium, the same strain being inhibited by 0.05 microgm. of the drug per cubic centimeter in either medium.[2]

Other significant contributions to an understanding of the action of isoniazid have come from the Departments of Pharmacology and of Medicine at the University of Chicago, where studies were carried out with the aid of isotopic, C^{14}-labeled isoniazid. This technic provides an extremely sensitive and relatively simple method of determining small amounts of drug and its metabolites in tissues and body fluids. In preliminary studies in mice[3] the isotope-labeled drug was found to be localized chiefly in the liver, spleen, lung, brain and kidneys. The lung was found to contain significant amounts of activity even after the blood level had fallen to only trace amounts. Both isonicotinic acid hydrazide and its major metabolite, isonicotinic acid, were found in brain tissue. The skin appeared to serve as a major storage depot of the drug, and the urinary system as its major pathway of excretion. Less than 1 per cent of the injected drug was converted into carbon dioxide.

The same method was used to determine the distribution and excretion of isoniazid in tuberculous patients.[4] Peak levels were reached in the blood and plasma within an hour of intramuscular injection. Levels fell rapidly during the first eight hours, but measurable quantities of drug were found in blood and plasma three to seven days after a single injection. Isoniazid was shown to be freely diffusible and was found in appreciable amounts in uninfected tissues and body fluids, including uninfected spinal fluid of patients with tuberculosis. Here, again, the highest concentrations were found in lung and skin, and the drug was excreted chiefly by the kidneys, small amounts being excreted in the feces, or by the lungs as carbon dioxide. It was also shown that the isoniazid diffused freely into dense caseous lesions in both lung and lymph nodes and was present there in high concentrations three to five hours after injection. The drug was also found in pleural fluid in high concentration two and a half hours after injection, and measurable quantities remained three days later.

In an attempt to clarify the antibacterial effect on tubercle bacilli, quantitative studies were made of the bacterial growth and of the uptake of C^{14}-labeled drug by the organisms during growth.[5] These studies showed that isoniazid had a delayed effect on the susceptible tubercle bacilli, the initial action being bacteriostatic rather than bactericidal; massive quantities of the drug were no more effective than smaller quantities. By contrast, streptomycin had an immediate effect on the growth of the tubercle bacilli, and large amounts of streptomycin resulted in the death of more bacilli than when smaller quantities were used. There was a suggestion from these studies that isoniazid produced bacteriostasis by interfering with the formation of some essential metabolite. Tubercle bacilli susceptible to isoniazid became radioactive when grown in a medium containing C^{14}-labeled isoniazid, whereas isoniazid-resistant tubercle bacilli did not become radioactive when grown in a similar medium.

Thus, the favorable distribution of isoniazid in the body, its penetration into and high activity against intracellular organisms and its persistence in tissues that are particularly vulnerable to the tubercle bacillus, as well as the incorporation of the drug into the susceptible bacilli, add considerably to an understanding of how this important drug acts. The failure to find the isotopic-labeled drug in the isoniazid-resistant tubercle bacilli and its demonstration in the sensitive organism suggests that the bacteriostatic effect on susceptible organisms results from the interference by the drug with the formation of some essential metabolite by the organisms. These studies do not provide any clue to how to overcome one of the major deficiencies that isoniazid shares with streptomycin — namely, the property of rapidly inducing high degrees of resistance in initially susceptible tubercle bacilli.

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TRANSPLANTATION BULLETIN

This month a new and exceptional addition to the specialty journals is expected to appear. *Transplantation Bulletin*, a quarterly devoted to the rapid and informal exchange of information in the field of tissue transplantation, will not be a journal in the usual sense of a periodic collection of formal articles. Rather, its purpose will be, by means of brief comments on problems in the field, to keep its readers informed of advances in tissue transplantation and of forthcoming meetings of professional societies at which any aspect of transplantation will be considered. To this end, the *Bulletin* will maintain and publish yearly a registry of all practicing physicians and research workers in the United States and abroad who are primarily or incidentally concerned with tissue transplantation through their work in plastic surgery, endocrinology, cancer, genetics, immunology, morphology and so forth. In addition, it will maintain a bibliography of published work in these fields.

The managing editors include Herbert Conway, M. D., of Cornell University Medical College, Ernest J. Eichwald, M. D., of University of Utah College of Medicine, and Nathan Kaliss, Ph.D., of the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine. Blair O. Rogers, M. D., of Columbia University College of Physicians and Surgeons, will be associate editor.

To the new arrival — an exotic in the field of scientific publishing, in which there appears always to be room for one more — the *Journal* extends a warm welcome.

SPECIAL ASSISTANT ON HEALTH AND MEDICAL AFFAIRS

The appointment of Chester Scott Keefer to be a special assistant to the Secretary of Health, Education and Welfare does credit to the wisdom of the administration.

A graduate in medicine of Johns Hopkins University, Dr. Keefer, a former member of the editorial board of the *Journal*, has been physician-in-chief of the Massachusetts Memorial Hospitals and Wade Professor of Medicine at Boston University School of Medicine since 1940. During World War II he was chairman of the Committee on Therapeutics of the National Research Council and had charge of administering the distribution of penicillin.

He has been chairman of the Committee on Investigation of Cortisone for the National Academy of Sciences, a member of the editorial boards of *Antibiotics and Chemotherapy* and the *American Practitioner* and stands in a position to bring sound medical advice to lay administrators.

Dr. Barron, formerly of Palmer, who has been for some time past digging for a mineral spring at Ballston, N. Y., by "spiritual direction," has been successful after digging some 18 feet; most of which distance was through solid rock.

Boston M. & S. J. *August 17, 1853*

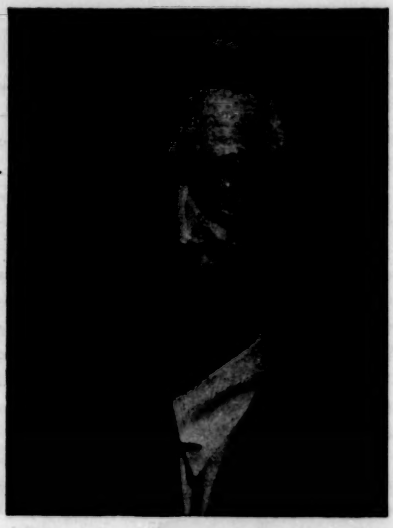
MASSACHUSETTS MEDICAL SOCIETY

FRANK HOWARD LAHEY

1880–1953

Frank Howard Lahey, son of Thomas and Honora Frances (Powers) Lahey, was born in Haverhill, Massachusetts, on June 1, 1880, and died in Boston on June 27, 1953.

Dr. Lahey was educated in the Haverhill public schools, Harvard College and Harvard Medical



School (M.D. 1904). The honorary degree of Doctor of Science was conferred on him by Tufts College in 1927, by Boston University in 1943, and by Northwestern University in 1947.

Dr. Lahey's only survivor is his wife whom, as Alice Wilcox, he married on April 15, 1909. Their life together of forty-four years was one of unfailing happiness and mutual devotion.

After graduation from medical school he served as intern at the Boston City Hospital, resident surgeon of the Haymarket Square Relief Station and surgeon of the Long Island Hospital. From the beginning his extraordinary surgical skill was recognized and it was not many years after he started practicing in Boston before his name was linked with other great American surgeons of international renown.

An early interest in surgery of the thyroid remained with him throughout his life. He was the first Boston surgeon to make use of the basal-metabolism test as an index of thyroid toxicity. He developed a two-stage operation that, in his hands and those of his pupils, brought safety to what had been one of the gravest surgical risks. Later he became equally renowned for his surgery of the gastrointestinal tract and the gallbladder, his skill bringing hundreds of surgeons, old and young, from all parts of the world to see him operate and to share with him the knowledge and experience he was always ready to pass on to others with simplicity, generosity and modesty.

In 1922 Dr. Lahey gathered around him a small group of physicians who were to become the nucleus of what is now the Lahey Clinic. The assistant surgeon was the late Howard M. Clute, the anesthetist, the late Lincoln F. Sise, and the gastroenterologist, Sara M. Jordan, who is the only survivor of this small group. An early member of the team was Miss Blanche Wallace, Dr. Lahey's surgical nurse for over thirty years.

In January, 1926, the first unit of the Lahey Clinic was opened at 605 Commonwealth Avenue. At this time there was a great debate in the medical world about group medicine. Many physicians thought that group medicine would impair doctor-patient relations but Dr. Lahey believed and demonstrated that group medicine could be administered without destroying these relations or impairing the individual responsibility of members of the group to their patients. He was an unusually competent administrator but even as the operations of the Clinic and the variety of the services grew in complexity, he never forgot its obligations to the poor and the unfortunate, and in that respect as in all others lived up to the highest standards of the profession. His tenderness to the very young, the very old and the desperately sick revealed the natural kindness of heart that supplemented his skill as a great physician.

Dr. Lahey was an inspiring teacher. In his early years he was an instructor in surgery at the Harvard Medical School and later became professor of clinical surgery there; he was also assistant professor and later professor of surgery at Tufts College Medical School. He was the author of many scientific papers and was one of the most forceful and popular speakers on the medical lecture platform. His greatest contribution to the education of others was in the course of his day-to-day practice where by practical

precept and superb example he imparted to his assistants and to those who had come to watch him lessons that, he said with his usual candor, he had learned from his failures as well as his successes.

From the revenues of the Clinic and from other sources, the Lahey Foundation, devoted to medical research and education, was established by him. Among other contributions to medical education was his service as a member of the Council on Scientific Assembly and the Council for Medical Education and Hospitals of the American Medical Association.

During World War I Dr. Lahey served as a major in the Medical Corps of the United States Army and as director of surgery at Evacuation Hospital No. 30 in France. In World War II he was chairman of the Procurement and Assignment Commission, which directed the enlistment and assignment of physicians needed in the war effort. After this service he was made honorary consultant to the Medical Department of the United States Navy.

Throughout his life he was a consistent and powerful opponent of socialized medicine and was not in sympathy with the partial socialization that has been brought about by the Government operation of hospitals and medical services for veterans; he advocated an insurance system instead.

Dr. Lahey's services to the associations of his profession and the honors conferred on him by them are without number. He was president of the American Medical Association in 1942; regent of the International College of Surgeons at Geneva; Fellow of the American College of Surgeons (Board of Governors), Honorary Fellow of the Royal College of Surgeons in England; member of the American Surgical Association; member of the American Association for the Study of Goitre; member of the Société des Chirurgiens de Paris, and many other American and international surgical associations. In the space of a few weeks in 1946 he received the Legion of Honor, the Bigelow Medal and the Friedenwald Medal of the American Gastroenterological Association.

On the occasion of his sixtieth birthday, June 1, 1940, a birthday volume sponsored by friends and patients was presented to him by his colleagues in the Clinic and elsewhere, which includes important and interesting scientific papers and many expressions of admiration and affection.

Dr. Lahey was a generous contributor to Boston hospitals and solicited many contributions to them from his patients and friends. A new building to be dedicated this fall at the New England Baptist Hospital where he operated so many years and where he died, largely financed through his efforts, will be known as the Lahey Pavilion. He had a deep interest in the Boston Medical Library and, because of his interest, all staff members of the Clinic were made fellows. Plans have now been completed by the staff members to finish and furnish the periodical room, which will bear in his honor the name "The Frank H. Lahey Periodical Room."

An early avocation was his interest in dog field trials in which dogs that he owned had much success. He found this too time consuming and substituted for it another out-of-door sport, golf, that he could share with Mrs. Lahey. When his game was good it was considerably better than average, but often it was bad. Then his comment was that he was glad he could return to his surgery, that he was sure he could do better than golf.

Dr. Lahey was eulogized in the Congress of the United States on July 9, 1953. To one sentence of that eulogy, "The world has lost a man who was unequaled in his services to mankind," his friends would add that they have lost the force, kindness and magnetism of a great personality, but that memories of a rare friendship will be forever cherished.

DISASTER RELIEF NEEDED

The tornado that struck the Worcester area on June 9, 1953 caused extensive property damage, serious injury and loss of life.

Physicians, nurses, other health workers and the hospitals in the disaster area rendered outstanding service to the hundreds of injured. This service was immediate and it has been continuous. Professional and other services were immediately offered from other areas. Because of the efficient and competent medical services available in the Worcester area, the outside help required was minimal.

But the millions of dollars of loss in homes and property present a serious need that has not yet been met. Governor Christian A. Herter, through Lieutenant Governor Sumner G. Whittier, has organized the Central Massachusetts Disaster Relief Committee, Inc. This committee has been charged with the responsibility of urging more fortunate citizens of the Commonwealth to assist in the immediate and necessary work of rehabilitation in the tornado area.

The financial assistance of physicians has been requested. The need is great. The co-operation of individual physicians is urged. Contributions should be sent to the Central Massachusetts Disaster Relief Committee, Inc., Worcester City Hall, Worcester, Massachusetts.

DONALD E. CURRIER
CHARLES H. BRADFORD, *Chairmen*
Committee on Emergency Medical Service

SECRETARY'S NOTE

A copy of the *Circular of Advance Information for Councilors*, containing committee reports to be considered at the October 7 meeting of the Council, will be sent to any fellow on request to the Secretary, 22 Fenway, Boston, before August 20, 1953.

ROBERT W. BUCK, M.D., *Secretary*

BOSTON MEDICAL LIBRARY

CIBA SERIES

Ciba Symposia, the English edition of *Ciba Zeitschrift*, was discontinued with the fall number of volume 11 for 1951. This series, although not so indicated by its name, is a valuable periodical on the history of medicine and related subjects. All the covers of the various numbers are devoted to portraits or medical sciences and should be retained in binding. The first number of the first volume was issued in April, 1939. The English edition is common, but the *Union List of Serials* does not list a complete set of the *Zeitschrift* in the United States, or Canada, although the Library has a complete run. A companion series, the *Ciba Rundschau*, of similar excellence, began in May, 1936. It is devoted to the history of industry and technology. It was also issued in an English edition under the title of *Ciba Review*.

HEBREW MEDICINE

Attention is called to an unusual periodical, published quarterly in Paris: *Revue d'histoire de la médecine hébraique*. It began publication in June, 1948, and 15 numbers were published to December, 1952. An index for 1948–1951 was issued as a supplement. Dr. I. Simon, of Paris, is the editor. It is the organ of the Société d'histoire de la médecine hébraique. The first number contained articles by Dr. Simon on the history of Hebrew medicine from its origin to the present day, and on history and activities of the society. A set is in the Boston Medical Library.

CORRESPONDENCE

"TRUTH STILL THE LIGHT"

To the Editor: I was much interested in Dr. Frank A. Howard's letter on the art of medicine in the June 11 issue of the *Journal*.

Many patients are undoubtedly frightened by incautious, verbose and often highly technical talk on the part of the physician. But on the other hand, many are dissatisfied and often bewildered on receiving no explanation after a thorough examination, a multitude of tests and x-ray films and an assortment of drugs.

The science of medicine has reached the stage where a specific diagnosis can be given in most cases. Most patients are thoroughly aware of this, owing to mass education and facility of communication. They expect a reasonable explanation of their aches and pains. I have seen many who have gone from one doctor to another — not because they did not receive effective therapy, but because they did not receive any explanation of their illness.

Even the average intelligent person, on feeling bodily discomfort, is beset by fears of heart attack, stroke, cancer and so forth. It is not sufficient to examine a patient with epigastric distress and tell him that there is nothing seriously wrong and prescribe a diet and antacids. Is the patient not entitled to even a simple explanation of the physiology of gastric acidity and motility and its relation to epigastric distress, high-tension living, heavy smoking and bad dietary habits? Will not this produce a better patient-doctor relation and more effective therapy?

I believe that some of the present dissatisfaction and criticism of medical practitioners is due to the attitude of many physicians that the patient is not intelligent enough to understand his illness and requires no explanation. Doctors can raise as many doubts and fears in patients by saying too little as they can by saying too much.

A. E. Robin, M.D.

Minitonas, Manitoba

NONCLINICAL NOTES

AMERICAN COLLEGE OF CARDIOLOGY

Dr. Robert P. Glover, clinical professor of surgery, Hahnemann Medical College and Hospital, Philadelphia, was recently installed as president of the American College of Cardiology at its second annual meeting in Washington, D. C. Dr. Ashton Graybiel, director of research, United States Naval School of Aviation Medicine, Pensacola, Florida, was chosen president-elect. Officers elected for the year 1953-54 were as follows: David Bruce Dill, Ph.D., Dr. Hubert Mann, and John C. Krantz, Jr., Ph.D., vice-presidents; Dr. Philip Reichert, secretary; Dr. Seymour Fiske, treasurer; Dr. Simon Dack, assistant secretary; Dr. William L. Wheeler, Jr., assistant treasurer; and Dr. Irving Brotman, Dr. George W. Calver and Dr. Joseph P. Harvey, trustees for two years.

BEAUMONT MEMORIAL

The February, 1953, number of the *Journal of the Michigan State Medical Society* is devoted in part to Dr. William Beaumont and his pioneer work on the physiology of digestion. There are seven papers, concerned with the memorial on Mackinac Island, Michigan, to be completed in 1953. The old retail store of the American Fur Company was purchased by the Michigan State Society, and when the restoration is finished, the property will be given to the Mackinac Island State Park Commission of Michigan for preservation. The leading article by Dr. Alfred H. Whittaker, chairman of the restoration committee, presents a long account of Dr. William Beaumont and his experiments with Alexis St. Martin. The papers have been reprinted in a pamphlet under the title of the *Beaumont Memorial Number*. The cover is a reproduction in color of the well known painting by Dean Cornwell, called "Beaumont and Alexis St. Martin."

NOTICES

SECOND INTERNATIONAL CONGRESS ON HIPPOCRATIC MEDICINE

The Second International Congress on Hippocratic Medicine will be held at Evian, Switzerland September 3-6. The sessions will be divided into five parts, on pathology, constitutional medicine, hygiene and therapeutics, surgery, and sociology in relation to medicine. Professor Laignel-Lavastine, of Paris, is president, and there are seven vice-presidents, from Brazil, England, France, Spain, Italy and Greece. There are four classes of members, for physicians, associated professions, interns and students, and the wives of members.

SOCIETY MEETINGS AND CONFERENCES

August 18-21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.
September 3-6. Second International Congress on Hippocratic Medicine. Notice above.
September 23. Middlesex South District Medical Society. Page 260, issue of August 6.
September 24–October 1. Fourth Congress of Pan American Medical Women's Alliance. Page 124, issue of July 16.
October 4-9. American Academy of Pediatrics. Page 1126, issue of June 25.
October 5–December 21. Hartford Medical Society Program. Page 260, issue of August 6.
October 12-14. National Gastroenterological Association. Page 260, issue of August 6.
October 12-17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.
October 15-17. Annual Course in Postgraduate Gastroenterology. Page 260, issue of August 6.

(*Notices concluded on page xvii*)